Original Contribution

Modafinil May Alleviate Poststroke Fatigue
A Randomized, Placebo-Controlled, Double-Blinded Trial

Mai Bang Poulsen, MD; Bodil Damgaard, MD; Bo Zerahn, MD; Karsten Overgaard, MD; Rune Skovgaard Rasmussen, MA, PhD

Background and Purpose—Poststroke fatigue is common and reduces quality of life. Current evidence for intervention is limited, and this is the first placebo-controlled trial to investigate treatment of poststroke fatigue with the wakefulness promoting drug modafinil.

Methods—The trial was randomized, double-blinded, and placebo-controlled. Patients were treated with 400-mg modafinil or placebo for 90 days. Assessments were done at inclusion, 30, 90, and 180 days. The primary end point was fatigue at 90 days measured by the Multidimensional Fatigue Inventory-20 general fatigue domain. Secondary end points included the Fatigue Severity Scale, the Montreal Cognitive Assessment, the modified Rankin Scale and the Stroke-specific quality of Life questionnaire. Adult patients with a recent stroke achieving a score of ≥12 on the Multidimensional Fatigue Inventory-20 general fatigue domain were consecutively included. Exclusion criteria were severe cognitive disabilities and contraindications for modafinil treatment.

Results—One thousand one hundred twenty-one patients with stroke were screened and 41 patients included, 21 received modafinil. The primary end point, the Multidimensional Fatigue Inventory-20 general fatigue score, did not differ between groups. Patients in the modafinil group obtained better scores on the Fatigue Severity Scale (P=0.02) and in some subscales of the stroke-specific quality of life questionnaire ($0.001<P<0.05$), which were secondary outcomes. No serious adverse reactions were observed and there was no difference in blood pressure between groups.

Conclusions—There were no significant differences between the 2 groups with regard to the primary end point. There were secondary significant outcomes that should be explored in future trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01800097.

(***Stroke*. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.010860.)**

Key Words: clinical trial ■ fatigue ■ randomized controlled trial ■ rehabilitation ■ stroke

Fatigue is common among patients with stroke. Frequencies range from 35% to 92%, although highly dependent on definition, time, and method for assessment.[1,2] Poststroke fatigue influences quality of life negatively, and is associated with a poorer physical health 18 months after stroke, later return to work and a higher risk of death.[3–6] Furthermore, poststroke fatigue has been rated by patients among the top 10 research priorities relating to life after stroke,[7] and 40% of stroke survivors reported fatigue as one of the worst consequences within the first year after their stroke.[8] Therefore, interventions against poststroke fatigue are warranted. Physical, cognitive, and medical strategies have been proposed but to date there is little evidence to guide clinical practice.[9]

Factors such as depression, anxiety, higher age, female sex, cognitive impairments, and prestroke fatigue are thought to be associated with poststroke fatigue but causal relationships have been difficult to establish.[10] Depression has been studied most intensively, and although there is strong evidence linking fatigue and depression, there is also evidence that fatigue occurs without depression.[11] Two trials have addressed treatment with antidepressive medication for fatigue after stroke but found no effect.[12,13]

Modafinil is a wake promoting drug useful for treatment of excessive sleepiness in narcolepsy, shift work sleep disorder, and obstructive sleep apnea. Numerous other indications, including treatment of fatigue in multiple sclerosis, have been suggested but are still debated.[14] The neurobiochemical effects of modafinil are complex and not fully understood.[15] The primary effects seem to involve inhibiting reuptake by dopamine and norepinephrine transporters. Furthermore, it is known to have some effects on serotonin, glutamate, gamma-aminobutyric acid, orexin, and histamine systems, but it is unknown

Received July 16, 2015; final revision received September 24, 2015; accepted September 29, 2015.

Departments of Neurology (M.B.P., K.O., R.S.R.), Radiology (B.D.), and Clinical Physiology (B.Z.), Herlev University Hospital, Herlev, Denmark; and Department of Radiology, Hilleroed University Hospital, Hilleroed, Denmark (B.D.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.010860/-/DC1.

Correspondence to Mai Bang Poulsen, MD, Department of Neurology, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark. E-mail maibang@gmail.com

whether these effects are direct or a consequence of changes in the catecholamine system.[16] The pharmacological profile is distinct from amphetamine,[17] and modafinil has fewer adverse effects, little potential for abuse and no withdrawal reactions.[18]

Higher frequencies of adverse reactions in patients treated with modafinil than placebo have been reported in clinical trials.[14] The most common are headache, nausea, insomnia, and nervousness. A concern about modafinil has been a high rate of dermatologic reactions in patients with attention deficit hyperactivity disorder.[14]

To our knowledge, modafinil has only been used for poststroke fatigue treatment in a small trial without placebo control.[19] The aim of this study was to evaluate the effect of treatment with modafinil on fatigue after stroke. The primary end point was to reduce fatigue measured by the general fatigue domain on the Multidimensional Fatigue Inventory-20 general fatigue domain (MFI-20 GF), whereas secondary end points included improvements on the Fatigue Severity Scale (FSS) and of neurological outcome, quality of life, cognition, reaction times, depression, bone density, and muscle mass.

Methods

The trial was a phase 3, single-center, randomized, double-blinded, and placebo-controlled trial. Patients were assigned 1:1 to modafinil or placebo.

Study Population

Patients were recruited from the Department of Neurology at Herlev Hospital, Denmark, Included patients had had a stroke within 14 days; had a modified Rankin Scale score of ≤3 before admission; and were at least 18 years old. They experienced poststroke fatigue, with a score of ≥12 on the MFI-20 GF and gave written informed consent to participate. Exclusion criteria were cognitive or communicative disabilities that would substantially affect a patient's ability to answer questionnaires; fertile women not using safe contraceptives; other disorders known to give substantial fatigue (including any malignant disease); continued treatment with benzodiazepines or antiepileptic drugs (not including sleeping pills); and stroke induced by infection, trauma, or surgery, or a contraindication for modafinil treatment (including drug or alcohol abuse).

From January 2014, the inclusion criterion about stroke within 14 days was expanded to 6 months to increase recruitment.

Screening Procedure

Patients admitted to the Department of Neurology with a stroke diagnosis were consecutively screened. All patients complying with in and exclusion criteria were approached and presented with the MFI-20. For patients not eligible for inclusion, the reason was recorded. If >1 reason applied, only the first on the list was recorded. If they had a score of ≥12 on the MFI-20 GF, they were offered inclusion in the study. All enrollments and all assessments were conducted by 1 investigator blinded to modafinil treatment.

Randomization, Blinding Procedure, And Treatment

Patients were treated with 400-mg modafinil or placebo in 100-mg tablets for 90 days. The dose was reduced to 200 mg if the patient was ≥65 years. The treatment was administered in the morning. If assumed adverse events were encountered, a dose reduction was allowed.

Patients were assigned on site to either placebo or modafinil according to a computer-generated plan with permuted different block sizes. The plan was generated at www.randomization.com by the associated unblinded study nurse. Block sizes were kept unknown to all blinded staff. Medication was individually allocated according to this plan by the unblinded study nurse. All medication allocations were double checked by another unblinded person. Medication containers were only identifiable by a number referring to a medicine identification list. The medicine identification list was only available to unblinded staff who prepared the medication, and they had no contact with the included patients. The medication and the medication identification list were prepared by an independent pharmacy holding the necessary permits.

Outcome Assessment

Patients were evaluated at baseline and at 30, 90, and 180 days. Medication ended after the 90-day visit. The MFI-20 questionnaire was completed at all 4 visits. It is a 20-items fatigue self-administered 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 up to a total domain score. The MFI-20 GF domain can be used as an overall measure of fatigue.[20]

The secondary end points described in the following were obtained at all 4 visits. First, we used the FSS that is a 9-item self-administered questionnaire originally developed for measurements of fatigue in multiple sclerosis and systemic lupus erythomatosus. Each item is scored from 1 to 7 with higher scores reflecting more fatigue. The median of all items gives a global score.[21] After initiation of this study, the scale was validated in a stroke cohort showing better results if items 1 and 2 were removed.[22] Therefore, we have included both versions of the scale. We refer to the reduced form as FSS-7. For measurements of disability, we used the modified Rankin Scale, the modified Barthel-100 Index, and the Scandinavian Stroke Scale. The modified Rankin scale describes disability on a scale from 0 to 6 where 0 indicates no symptoms at all and 6 indicates death.[23] The modified Barthel-100 Index is a scale measuring 10 variables describing activities of daily living. The maximum and best score is 100.[24,25] Scandinavian Stroke Scale is a scale to measure neurological disabilities after stroke. A maximum score of 58 is obtained if the patient has no symptoms at all.[26] As measurements of physical performance, we used the 30-s chair to stand test and the timed up and go test. The 30-s chair to stand test is a test of lower body strength. Patients with arms held bended and against the chest were asked to rise from a chair and sit down again as many times as possible within 30 s. A 17″ chair without armrests was used, placed with the back against a wall.[27] The timed up and go test is a test of mobility. It measures the time it takes for a person to rise from a chair, walk 3 m and return to the chair.[28] Further body composition in terms of bone mineral density, fat-free mass, and fat mass was obtained by dual-energy x-ray absorptiometry. Fat-free mass is a measure of total muscle mass. Scans were performed by a Lunar iDXA scanner with serial number DF+13189 and software version 14.10 (GE Medical Systems, Madison WI). Scanning was performed at inclusion and at 90 days. The idea was that patients who were less fatigued would be more active and, therefore, obtain a higher bone mineral density and more muscle mass. We measured reaction time by a simple procedure to obtain an overall measure of information processing speed.[29] The patient was placed in a quiet room and instructed to press a button as fast as possible when hearing a 500-Hz tone. The tone was generated from a computer program designed to give 150 auditory tones with random intervals ranging from 1 to 5 s between each tone. If the tone was not interrupted by a press on the button it ended after 1000 ms. Patients were allowed a total of 5000 ms to respond from the start of the tone. Failure to respond within these 5 s was registered as an error (missing response). Responding too early (before 100 ms) was also registered as an error (immature response), thus correct responses were accepted within the range of 101 to 4999 ms. We measured the median reaction time, the number of immature responses, and the number of mistakes as end points. The program was designed by Gary Darby (http://delphiforfun.org, VA).

At 30, 90, and 180 days visits the following outcomes were added: Major Depression Inventory, The Stroke-Specific Quality of Life (SS-QoL) scale, and the Montreal Cognitive Assessment. The Major Depression Inventory is a 10-item self-report questionnaire with dual functions. A total score indicates the degree of depression although it also contains the information necessary for making a diagnosis of depression according to the 10th revision of the *International Statistical Classification of Diseases* and related health problems.[30] A higher score indicates a greater burden of symptoms. The SS-QoL Scale is an instrument developed to evaluate health-related quality of life in patients with stroke. It is divided into 12 domains, and each domain consists of 3 to 6 questions. Questions are scored from 1 to 5 and the scores within 1 domain are summarized into a domain score where higher scores indicate better quality of life.[31,32] The Montreal Cognitive Assessment is a short cognitive screening tool designed to detect cognitive impairments. The maximum score is 30 and a score of >26 is considered normal.[33] It has been validated for patients with stroke recently.[34]

The outcome measurements of physical performance (timed up and go test, chair to stand test, and body composition) were omitted for patients included later than 14 days because they were no longer expected to improve in these parameters.

All adverse events were registered by interview and review of patient files at each visit. Events were followed closely by the external monitoring unit. An annual safety report was handed in to the Danish Health authorities.

Statistics

To detect a difference in mean MFI-20 GF scores of 2 points, we should include 64 patients in each group if Z2-α and Z-β (type 1 and type 2 errors) were 5% and 20%, respectively and the SD of the MFI-20 GF was 4 (www.statstodo.com/SSiz2Means_Pgm.php). Because of small groups, data were not assumed normally distributed and measured as medians with associated interquartile ranges unless otherwise stated.

Comparisons of groups were done with Mann–Whitney *U* test for nonpaired groups, and proportions were compared with Fisher exact test. Statistics were calculated with IBM SPSS version 22. Data were analyzed blinded to treatment allocation.

Ethics

The trial was registered at clinicaltrials.gov with unique identifier: NCT01800097. The full protocol is only available in Danish. The trial was approved by the Danish Data Protection Agency (2007-58-0015/HEH.750.87–1), the National Health and Medicines authority (23349) and by the Regional Committee on Health Research Ethics (H-3-2009-116). The trial was monitored by the unit for Good Clinical Practice at Copenhagen University Hospital. All patients provided written informed consent.

Results

Between October 2012 and October 2014, we screened 1121 patients and 41 patients were included. The last follow-up visit was conducted by the end of March 2015. Twenty-one were allocated to modafinil treatment. Data on the primary end point were available for 17 in the modafinil and 18 in the placebo group; see details in Figure (flow chart). From 90 to 180 days, 4 patients withdrew from the study. One moved to a distant location and 3 could no longer manage to come for the visit. Some of the secondary outcomes were not obtained in all cases because the patients were fatigued. Only mobile patients could do the timed up and go test and the 30-s chair to stand test.

The study recruited fewer patients than planned within the scheduled timeframe because of a lack of eligible patients. It was not possible to extend the recruitment period because of lack of funding.

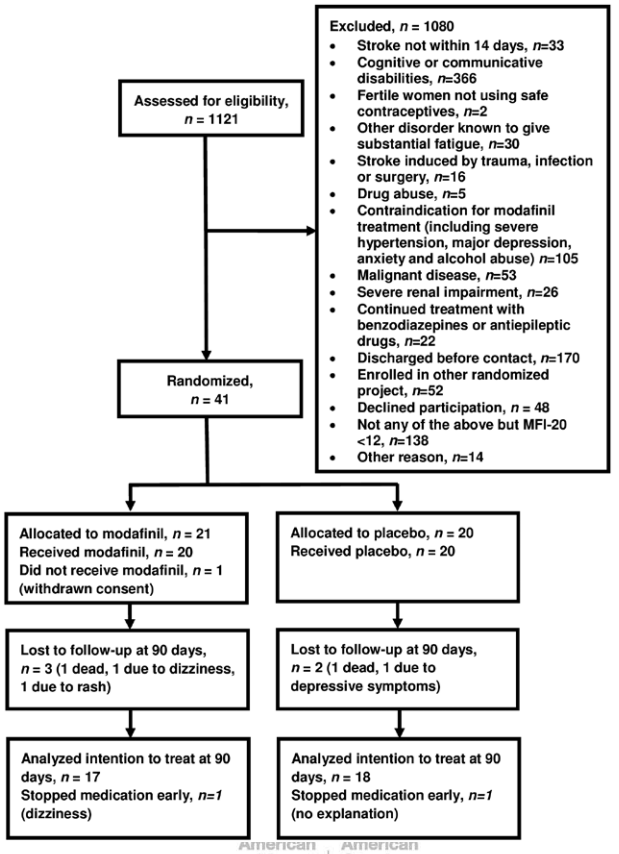

Figure. Flowchart.

Baseline characteristics for included patients are presented in Table 1. No difference between the modafinil and the placebo group was detected in 35 variables except for the timed up and go test where the modafinil group performed significantly better than the placebo group. The treatment dose was reduced to 200 mg because of age in 14 of 21 patients in the modafinil group (67%) and in 16 of 20 in the placebo group (80%). Two patients in the modafinil group (9.5%) and 4 patients in the placebo group (20%) were included after 14 days from the index event.

Outcomes at 90 days are shown in Table 2. Change in scores between inclusion and 90 days are shown in Table 3. Score changes are positive if they represent an improvement and negative if they represent a worsening.

After 90 days, the MFI-20 GF median score was 27% higher in the placebo group than in the modafinil group (P=0.31). From baseline to 90 days, the MFI-20 GF median score decreased 25% more in the modafinil group, although these differences were not significant. None of the other subscales of the MFI-20 questionnaire differed significantly between groups.

The FSS showed significantly better scores in the modafinil group at 90 days regardless of whether the full FSS or the shortened FSS-7 was used ($0.01<P<0.05$). The decrease on the FSS from inclusion to 90 days was also significantly better in the modafinil group for both versions of the scale ($0.01<P<0.05$). There was no significant difference between the groups in MFI-20 or FSS scores at 30 or 180 days except

Table 1. Baseline Health Characteristics

	Modafinil (n=21)	Placebo (n=20)
Age, y	69 (62–79)	71 (65–82)
Female sex (%)	10 (48)	12 (60)
Ischemic stroke (%)	20 (95)	17 (85)
Right hemisphere dominance (%)	19 (91)	19 (95)
Systolic blood pressure, mm Hg	139 (120–151)	132 (123–148)
Diastolic blood pressure, mm Hg	81 (72–92)	78 (70–93)
Heartrate, bpm	75 (65–87)	73 (62–80)
Right-sided stroke (%)	15 (71)	10 (50)
TACS (%)	2 (9.5)	1 (5)
PACS (%)	8 (38)	8 (40)
POCS (%)	8 (38)	7 (35)
LACS (%)	3 (14)	4 (20)
Current smoker (%)	5 (25)	6 (32)
Earlier smoker (%)	8 (40)	5 (26)
Hypertension (%)	9 (43)	13 (65)
Diabetes mellitus (%)	4 (19)	4 (20)
Earlier stroke (%)	6 (29)	4 (20)
Ischemic heart disease (%)	0 (0)	3 (15)
Time from stroke to inclusion (d)	8 (6–11)	9 (6–14)
Discharged to rehabilitation home (%)	10 (48)	10 (50)
MFI-20 GF	17 (16–19)	18 (15–20)
Fatigue Severity Scale	45.5 (37.8–57.5)	50.5 (37.8–54.8)
Fatigue Severity Scale-7	37.5 (26.5–45.3)	38 (29–45)
Scandinavian Stroke Scale	48 (31–54)	48 (44–54)
Modified Rankin score	3(2–4)	3 (2–4)
Barthel-100 score	86 (32–100)	86 (69–100)
Timed up and go test (s)*	9 (6–13), n=10	20 (9–37), n=11
Chair to stand test, no. of risings	2.5 (0–13), n=16	4 (0–8.3), n=16
Reaction time (ms)	339 (306–770)	407 (314–744)
Reaction time mistakes	3 (2–21)	2 (1–9)
Reaction time immature response	0 (0–5)	0 (0–2)
BMD (g/cm^2)	1.21 (1.196–1.301), n=7	1.12 (0.91–1.23), n=11
Fat mass (g)	30498 (29959–39585), n=7	20908 (16414–32905), n=11
Fat-free mass (g)	44965 (43395–59924), n=7	42654 (36776–57195), n=11

n (%) or median (interquartile range). BMD indicates bone mineral density; LACS, lacunar stroke; MFI-20 GF, Multidimensional Fatigue Inventory general fatigue domain; PACS, partial anterior circulation stroke; POCS, posterior circulation stroke; and TACS, total anterior circulation stroke.

*$P<0.05$.

that modafinil reduced mental fatigue in the MFI-20 mental fatigue subdomain at 180 days. These data are provided in the Table I in the online-only Data Supplement.

The results of the 12 domains of the SS-QoL questionnaire at 90 days are presented in Table 4. The domains of upper extremity function, work and productivity, and language were significantly better in the modafinil group.

At 30 and 180 days, there were several significant findings. The timed up and go test test and the SS-QoL domains of language, work and productivity, and energy were all significantly better in the modafinil group at 30 days ($0.01<P<0.05$). At 180 days, the SS-QoL domains of language and thinking were significantly better in the modafinil group ($0.01<P<0.05$). Exact data for 30 and 180 days can be found in the Table I in the online-only Data Supplement.

There was no significant difference between the 2 groups at any time in physical impairment measured by modified Rankin Scale score, modified Barthel-100 Index, chair to stand test, and the Scandinavian Stroke Scale or on depression or body composition measured by dual-energy x-ray absorptiometry scans.

There was no difference between the groups in reaction times for neither comparison between groups nor improvement scores. If both groups were combined into 1 group,

Table 2. Outcome Compared Between Groups at 90 days, Median (Interquartile Range)

	Modafinil (n=17)	Placebo (n=18)	*P* Value
MFI-20 general fatigue	11(10–15)	14 (10–16)	0.32
MFI-20 physical fatigue	11 (9.5–14)	13.5 (10–15.3)	0.29
MFI-20 reduced activity	11 (7–15.5)	15 (8.8–17)	0.13
MFI-20 reduced motivation	8 (4.5–9.5)	9 (7.8–11.5)	0.10
MFI-20 reduced motivation	7 (4.5–9.5)	9 (4.8–11.3)	0.39
Fatigue Severity Scale	36 (24–41)	49.5 (37–55)	0.019
Fatigue Severity Scale-7	22 (19–29)	37.5 (24.5–42.3)	0.042
Modified Rankin Scale	2 (1–4)	2 (2–3)	0.99
Scandinavian Stroke Scale	50 (36–57)	54 (49.8–56.5)	0.23
Barthel-100 Index	100 (62–100)	100 (98.5–100)	0.35
Timed up and go	6.5 (3.6–7.8), n=8	8 (5.3–12.5), n=12	0.098
Chair to stand	6 (0–15), n=12	11 (7–13), n=13	0.65
MoCA	25.5 (20.8–28), n=10	25.5 (23.5–28), n=16	0.86
MDI	7.5 (2.3–13.8), n=16	9.5 (6.5–16)	0.21
Reaction time, ms	356 (308–616), n=15	333 (287–485), n=18	0.23
Reaction time, immature responses	3 (1–7)	3 (0.75–5.25)	1
Reaction time, missing responses	1 (0–3)	0 (0–1.25)	0.14
Bone mineral density, g/cm^2	1.217 (1.188–1.275)	1.083 (0.916–1.204)	0.056
Fat mass, g,	27861 (26340–35239)	19895 (15985–31715)	0.15
Fat-free mass, g	45912 (41854–59148)	43338 (36269–59193)	0.43

If n differs from the number given in the top-row, it is stated beneath the outcome. MDI indicates Major Depression Inventory; MFI, Multidimensional Fatigue Inventory; and MoCA, Montreal Cognitive Assessment.

reaction times improved from inclusion to 90 days (*P*=0.004). Thus, both the groups achieved improved reaction times, but 1 group did not improve more than the other.

We then subtracted the 10th percentile reaction time from the 90th percentile reaction time to investigate if fatigue occurred more markedly at the end of the reaction time test. Again, we found no significant group differences on days 30, 90, or 180. We also compared the 90th with 10th percentiles improvement scores on days 30, 90, and 180 (all *P*>0.05).

Table 3. Change From Inclusion to 90 Days

	Modafinil (n=17)	Placebo (n=18)	*P* Value
MFI-20 general fatigue	6 (1 to 8)	4.5 (1.5 to 6.3)	0.44
MFI-20 physical fatigue	6 (1.5 to 8)	4 (–2.5 to 6)	0.80
MFI-20 reduced activity	4 (2 to 6.5)	2 (–1 to 4.75)	0.13
MFI-20 reduced motivation	2 (–4.5 to 3.5)	0.5 –4.3 to 5)	0.99
MFI-20 mental fatigue	1 (–1.5 to 4.5)	2 (0 to 6)	0.46
FSS	13 (–2.5 to 25.5)	–2 (–7.5 to 6.2)	0.04
FSS (7)	13 (–2.5 to 24)	–0.5 (–1.25 to 6)	0.047
Modified Rankin score	1 (0 to 1), n=18	1 (0 to 1), n=19	0.50
Scandinavian Stroke Scale	5 (2 to 13) n=15	3 (0 to 7.3)	0.46
Barthel-100 score	6 (0 to 35)	10 (0 to 26)	0.83
Chair to stand-test	0 (0 to 4.75), n=12	4 (1 to 8), n=13	0.07
Timed up and go	4 (0 to 6), n=7	10.5 (2.5 to 20.5), n=10	0.09
Reaction time, ms	7 (–41 to 160)	65 (10 to 156)	0.42
Reaction time, immature response	2 (–0.25 to 14.8)	0 (–3 to 7.5)	0.25
Reaction time, missing response	0 (–1.25 to 2)	0 (0 to 0)	0.74
Bone mineral density, g/cm^2	0.014 (0.0040 to 0.05), n=7	0.0095 (0.0085 to 0.029), n=11	0.79
Fat mass, g	3103 (2551 to 3841), n=7	1283 (–356 to 3776), n=11	0.21
Fat-free mass, g	–272 (–1107 to 911), n=7	–684 (–3032 to 356), n=11	0.25

Values illustrate the change in score between baseline and 90 days. If the value is positive, the value represents an improvement. If negative, it represents a worsening. FSS indicates Fatigue Severity Scale; and MFI, Multidimensional Fatigue Inventory.

Table 4. Median Stroke-Specific Quality of Life Scores (Interquartile Range) of the 12 Domains at 90 Days

	Modafinil, n=13	Placebo, n=17	*P* Value
Mobility	29 (26–30)	27 (24–30)	0.65
Energy	9 (6–12)	7 (4–12)	0.36
Upper extremity function	24 (22–25)	20 (17–24)	0.02
Work and productivity	14 (13–15)	12 (11–13)	0.007
Mood	22 (18–24)	21 (18–23)	0.46
Self-care	25 (22–25)	23 (22–25)	0.32
Social roles	19 (10–24)	13 (12–18)	0.32
Family roles	13 (9–15)	12 (9–15)	0.68
Vision	15 (15–15)	15 (14–15)	0.39
Language	25 (24–25)	22 (20–24)	0.012
Thinking	15 (12–15)	11 (8–15)	0.15
Personality	13 (12–15)	14 (11–15)	0.77

Comparing errors when performing the reaction time test, both groups made a similar amount of missing or immature responses on days 30, 90, and 180 (all $P>0.05$).

If the *International Classification of Diseases-Tenth Revision* diagnosis of depression is made on the basis of the Major Depression Inventory, there were 1 patient with a mild depression and 3 with a moderate depression at 30 days. Three of them were in the placebo group and 1 in the active group. At 90 days, none had depression and at 180 days 3 had a mild depression, 2 were in the placebo group, and 1 was in the active group. At 30 days, there was a trend toward better Major Depression Inventory scores among modafinil patients ($P=0.07$).

The number of overall events and serious adverse events are summarized in Table 5. There were no serious adverse reactions observed. Some of the most common events that could be related to the medication are included in Table 5. Eight patients stopped medication before 90 days; 3 of them because of assumed adverse effects: One patient experienced a rash, 2 experienced dizziness, and they were all seen in the modafinil group. The dose was reduced because of assumed adverse effects in 5 patients. Of these, 3 were in the modafinil group and 2 were in the placebo group.

The median blood pressure was 135/76 in the modafinil group and 134/78 in the placebo group at 90 days. The change in blood pressure from inclusion to 90 days did not differ between the 2 groups for neither the systolic blood pressure ($P=0.87$) nor the diastolic blood pressure ($P=0.47$). The median compliance was 99.5% in the modafinil group (98–100.8) and 99% (95.5–100.5) in the placebo group.

Discussion

This is the first placebo-controlled study of treating poststroke fatigue with modafinil. The trial did not recruit to target and was underpowered for the primary end point. There was no significant difference between the 2 groups with regard to the primary end point (the MFI-20 GF) neither when the groups were directly compared nor when the improvement from inclusion to 90 days was compared. After 90 days, fatigue was significantly reduced on the full and the shortened version of the FSS questionnaire, but this was a secondary end point.

There was a significantly better outcome for several domains of the SS-QoL questionnaire, especially the language domain was better at both 30, 90, and 180 days in the modafinil group. Throughout the study, all significant findings favored the modafinil group.

One other trial has addressed modafinil treatment for stroke but without placebo control. In that trial, investigators included 13 patients with brain stem or diencephalic stroke and 9 patients with cortical stroke. Investigators found a positive effect on patients with brain stem and diencephalic strokes, but not on patients with cortical stroke.[19] Because of different end points and the uncontrolled design, the effect size cannot be directly compared with our trial. Because of the few included patients in our trial, it did not make sense to compare patients with, for example, brain stem and cortical strokes.

Modafinil is structurally similar to methylphenidate.[35] A recent trial found methylphenidate to reduce mental fatigue in persons with traumatic brain injury,[36] whereas a similar fatigue reduction was not found in 2 randomized trials investigating effects of modafinil in patients after traumatic brain injury.[37,38] It would be reasonable to use methylphenidate instead of modafinil, although caution is advised for methylphenidate treatment in patients with cardiovascular disease because of effects on blood pressure.[39]

Another possibility for pharmacological fatigue treatment is the monoaminergic stabilizer drug OSU-6162, which has shown effect in reducing mental fatigue after traumatic brain injury in a cross-over designed study with 6 patients with stroke and 6 patients with traumatic brain injury.[40]

Modafinil is thought to enhance pattern recognition memory, digit span recall, and mental digit manipulation but it is debated whether there is an effect on spatial memory, attention, and other executive functions.[35] Effect on reaction time has been demonstrated in healthy sleep deprived individuals.[41] We did not observe an effect or even a trend toward improvement on general cognition as measured by the Montreal Cognitive Assessment test or on reaction time. A previous controlled trial of modafinil treatment for fatigue after traumatic brain injury also did not find effect using neuropsychological tests.[37]

The placebo-controlled and double-blinded design of the trial substantially reduced the risk of bias. The trial was conducted at a single center with a detailed screening log, and all patient contact was done by 1 person, thereby reducing

Table 5. Adverse Events

	Modafinil	Placebo
Serious adverse events	3	10
Headache	0	2
Dizziness	5	0
Restless legs	1	1
Dry eyes or mouth	5	2
Rash	2	0
Skin itching	0	2
Sleep disturbances	4	3
Overall no. of adverse events reported	55	63

observer variability. Data from the screening process could have been improved by recording the fatigue score of all screened patients.

The significant difference between the 2 groups at inclusion in the timed up and go test could indicate that the modafinil group had a higher physical performance level before treatment and it is possible that this influences the physical results in favor of the modafinil group. It should be noted that at baseline only 50% of the patients in each group were able to participate in this motor test (10 of 21 modafinil patients and 11 of 20 control patients), thus potentially providing a strong bias to these results.

Shortly after stroke and because of deteriorated health conditions, patients were not able to answer the depression and quality of life questionnaires, thus the later differences could have been present when the patients entered the trial.

The small number of included patients is a limitation, and the trial can only be interpreted as a pilot trial. The positive findings in the secondary end points should be interpreted carefully.

The inclusion criterion about time since the stroke was expanded during the trial. This allowed for inclusion of patients with a more chronic fatigue and made the patient population more diverse. It has been proposed that fatigue during the acute phase after stroke is different from fatigue at a later stage[10] and it has been proposed that different types of fatigue exist and should be addressed differently.[9] Therefore, a more diverse patient group could weaken the trial. Also, we defined fatigue by a score on the MFI-20 scale and it has been proposed that fatigue after stroke can be either an exertion fatigue or a chronic fatigue.[42] If different subtypes of fatigue were identified, it might have strengthened the study.

Adverse events were mild but relatively common in the trial. Fourteen percent of the patients allocated to modafinil treatment discontinued medication because of assumed adverse effects, whereas none of the patients in the control group did so. The earlier modafinil trial in patients with stroke had a dropout rate because of side effects of 25% despite a lower dosage.[19] Therefore, our use of the maximum allowed dose of 400 mg in patients aged <65 years does not seem to have had influenced the amount of adverse effects, but adverse events seem to be a consistent problem.

Future trials with modafinil for fatigue after stroke should closely monitor adverse effects. This trial does not give evidence for a clinical effect of treating fatigue after stroke with modafinil but the trend observed in the secondary end points are encouraging enough to merit further investigations.

Conclusions

Our trial is the first randomized, double-blinded, and placebo-controlled trial of poststroke fatigue treatment with modafinil. The trial was relatively small and must be interpreted as a pilot trial because it did not recruit to target. The trial was negative but there was a significant decrease in fatigue measured by the secondary outcome; the FSS, which should be explored in future studies. Treatment with modafinil was safe.

Acknowledgments

We are thankful to the Department of Neurology at Herlev Hospital for the tremendous support. Agnete Hviid Hornnes and Vesna Petrovic are thanked for their dedicated and careful help with the blinding procedure.

Sources of Funding

The trial was supported by the Danish Ministry of Higher Education and Science, the Department of Neurology at Herlev Hospital, The Health Foundation, The Research Council at Herlev Hospital, Merchant L.F. Foghts Foundation, Director Emil Hertz and wife Inger Hertz Foundation, Else and Mogens Wedell-Wedelsborgs Foundation, Boerge and Marie Kroghs Foundation, Soeren and Helene Hempels grant and the Linex Foundation. The drugs used was not supplied by the manufacturer but bought from an independent pharmacy.

Disclosures

None.

References

1. Mücke M, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L; Mochamat. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev*. 2015;5:CD006788. doi: 10.1002/14651858.CD006788.pub3.
2. Duncan F, Wu S, Mead GE. Frequency and natural history of fatigue after stroke: a systematic review of longitudinal studies. *J Psychosom Res*. 2012;73:18–27. doi: 10.1016/j.jpsychores.2012.04.001.
3. van de Port IG, Kwakkel G, Schepers VP, Heinemans CT, Lindeman E. Is fatigue an independent factor associated with activities of daily living, instrumental activities of daily living and health-related quality of life in chronic stroke? *Cerebrovasc Dis*. 2007;23:40–45.
4. 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.
5. Andersen G, Christensen D, Kirkevold M, Johnsen SP. Post-stroke fatigue and return to work: a 2-year follow-up. *Acta Neurol Scand*. 2012;125:248–253. doi: 10.1111/j.1600-0404.2011.01557.x.
6. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke*. 2002;33:1327–1333.
7. Pollock A, St George B, Fenton M, Firkins L. Top ten research priorities relating to life after stroke. *Lancet Neurol*. 2012;11:209. doi: 10.1016/S1474-4422(12)70029-7.
8. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Arch Phys Med Rehabil*. 1999;80:173–178.
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. Wu S, Mead G, Macleod M, Chalder T. Model of understanding fatigue after stroke. *Stroke*. 2015;46:893–898. doi: 10.1161/STROKEAHA.114.006647.
11. Choi-Kwon S, Han SW, Kwon SU, Kim JS. Poststroke fatigue: characteristics and related factors. *Cerebrovasc Dis*. 2005;19:84–90. doi: 10.1159/000082784.
12. Choi-Kwon S, Choi J, Kwon SU, Kang DW, Kim JS. Fluoxetine is not effective in the treatment of post-stroke fatigue: a double-blind, placebo-controlled study. *Cerebrovasc Dis*. 2007;23:103–108. doi: 10.1159/000097045.
13. Karaiskos D, Tzavellas E, Spengos K, Vassilopoulou S, Paparrigopoulos T. Duloxetine versus citalopram and sertraline in the treatment of post-stroke depression, anxiety, and fatigue. *J Neuropsychiatry Clin Neurosci*. 2012;24:349–353. doi: 10.1176/appi.neuropsych.11110325.
14. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs*. 2008;68:1803–1839.
15. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry*. 2006;67:554–566.
16. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*. 2008;33:1477–1502. doi: 10.1038/sj.npp.1301534.
17. Simon P, Hémet C, Ramassamy C, Costentin J. Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice. *Eur Neuropsychopharmacol*. 1995;5:509–514.

18. Rush CR, Kelly TH, Hays LR, Baker RW, Wooten AF. Acute behavioral and physiological effects of modafinil in drug abusers. *Behav Pharmacol*. 2002;13:105–115.
19. 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.
20. 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.
21. 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.
22. Lerdal A, Kottorp A. Psychometric properties of the Fatigue Severity Scale-Rasch analyses of individual responses in a Norwegian stroke cohort. *Int J Nurs Stud*. 2011;48:1258–1265. doi: 10.1016/j.ijnurstu.2011.02.019.
23. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
24. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol*. 1989;42:703–709.
25. Maribo T, Lauritsen JM, Waehrens E, Poulsen I, Hesselbo B. Barthel Index for evaluation of function: a Danish consensus on its use. *Ugeskr Laeger*. 2006;168:2790–2792.
26. Lindenstrom E, Boysen G, Christiansen LW, Hansen BR, Nielsen PW. Reliability of Scandinavian neurological stroke scale. *Cerebrovasc. Dis*. 1991;1:103–107.
27. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport*. 1999;70:113–119. doi: 10.1080/02701367.1999.10608028.
28. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142–148.
29. Meyer DE, Osman AM, Irwin DE, Yantis S. Modern mental chronometry. *Biol Psychol*. 1988;26:3–67.
30. Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord*. 2001;66:159–164.
31. Muus I, Williams LS, Ringsberg KC. Validation of the Stroke Specific Quality of Life Scale (SS-QOL): test of reliability and validity of the Danish version (SS-QOL-DK). *Clin Rehabil*. 2007;21:620–627. doi: 10.1177/0269215507075504.
32. Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. *Stroke*. 1999;30:1362–1369.
33. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695–699. doi: 10.1111/j.1532-5415.2005.53221.x.
34. Cumming TB, Churilov L, Linden T, Bernhardt J. Montreal cognitive assessment and mini-mental state examination are both valid cognitive tools in stroke. *Acta Neurol Scand*. 2013;128:122–129. doi: 10.1111/ane.12084.
35. Urban KR, Gao WJ. Performance enhancement at the cost of potential brain plasticity: neural ramifications of nootropic drugs in the healthy developing brain. *Front Syst Neurosci*. 2014;8:38. doi: 10.3389/fnsys.2014.00038.
36. Johansson B, Wentzel AP, Andréll P, Mannheimer C, Rönnbäck L. Methylphenidate reduces mental fatigue and improves processing speed in persons suffered a traumatic brain injury. *Brain Inj*. 2015;29:758–765. doi: 10.3109/02699052.2015.1004747.
37. Jha A, Weintraub A, Allshouse A, Morey C, Cusick C, Kittelson J, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil*. 2008;23:52–63. doi: 10.1097/01.HTR.0000308721.77911.ea.
38. Kaiser PR, Valko PO, Werth E, Thomann J, Meier J, Stocker R, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology*. 2010;75:1780–1785. doi: 10.1212/WNL.0b013e3181fd62a2.
39. Awudu GA, Besag FM. Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder: an update. *Drug Saf*. 2014;37:661–676. doi: 10.1007/s40264-014-0201-8.
40. Johansson B, Carlsson A, Carlsson ML, Karlsson M, Nilsson MK, Nordquist-Brandt E, et al. Placebo-controlled cross-over study of the monoaminergic stabiliser (-)-OSU6162 in mental fatigue following stroke or traumatic brain injury. *Acta Neuropsychiatr*. 2012;24:266–274. doi: 10.1111/j.1601-5215.2012.00678.x.
41. Wesensten NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *J Sleep Res*. 2005;14:255–266. doi: 10.1111/j.1365-2869.2005.00468.x.
42. Tseng BY, Billinger SA, Gajewski BJ, Kluding PM. Exertion fatigue and chronic fatigue are two distinct constructs in people post-stroke. *Stroke*. 2010;41:2908–2912. doi: 10.1161/STROKEAHA.110.596064.

Stroke
Journal of the American Heart Association

Modafinil May Alleviate Poststroke Fatigue: A Randomized, Placebo-Controlled, Double-Blinded Trial

Mai Bang Poulsen, Bodil Damgaard, Bo Zerahn, Karsten Overgaard and Rune Skovgaard Rasmussen

Stroke. published online November 3, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Supplemental Table I. Outcome compared between groups at 30 and 90 days, median (IQR). If n differs from the number given in the top-row, it is stated after the outcome.

	30 days			180 days		
	Modafinil (n=18)	Placebo (n=18)	P-value	Modafinil (n=14)	Placebo (n=16)	P-value
MFI-20 General Fatigue	15 (10.25 - 17.25)	15.5 (11 - 18)	0.82	13.5 (10.75 - 16.50)	14 (11 - 16)	0.85
MFI-20-Physical Fatigue	11.5 (8.5 - 18.25)	14 (11 - 18)	0.36	12.5 (8 - 15.25)	13 (10 - 15)	0.75
MFI-20-Reduced Activity	12.5 (10.75 - 17.75)	16 (12 - 18)	0.17	11.5 (6.5 - 13.25)	13 (10 - 15)	0.25
MFI-20-Reduced Motivation	8 (4.75 - 11)	9 (6 - 12)	0.39	7.5 (4.75 - 11)	7 (6 - 9)	0.81
MFI-20-Mental Fatigue	6.5 (4 - 13.25)	10.5 (5.75 - 13.50)	0.39	4.5 (4 - 9.25)	11 (5 - 13)	0.041
Fatigue Severity Scale	42.5 (26.5 - 50.25)	47.5 (31 - 53.75)	0.52	41(28 - 53)	47 (29 - 57)	0.54
Fatigue Severity Scale (7)	32.5 (17 - 41)	36 (24.25 - 41.5)	0.69	28 (21 - 39)	35 (21 - 44)	0.43
Modified Rankin Scale	3 (2 - 4)	2 (2 - 3)	0.41	2 (1 - 3.75)	2 (1.5 - 2)	0.85
Scandinavian Stroke Scale	52 (30.75 - 58)	52 (48.25 - 55.75)	0.56	55 (47 - 58)	55.5 (52.25 - 58)	0.74
Barthel-100 Index	100 (44.25 - 100)	100 (94.25 - 100)	0.44	100 (96 - 100)	100 (100 - 100)	0.46
Time up and go	7 (4 - 7.25), n=10	10.5 (7 - 13), n=10	0.01	6 (4 - 6.5), n=9	7 (5 - 10.5), n=10	0.16
Chair to stand	6 (0 - 14), n=16	9 (1 - 12), n=13	0.85	14 (0 - 16.50), n=13	12.5(10.75 - 15.25), n=10	1.00
MoCA	25 (20 - 28), n=11	27 (23 - 28), n=11	0.52	26 (23.5 - 29), n=12	27 (25 - 29), n=14	0.63
Major Depression Inventory	7 (4 - 13.5), n=17	16 (6 - 20.25)	0.083	8 (4 - 15), n=15	9 (7 - 23), n=15	0.74
Reaction time	363 (299 - 639), n=17	367 (290 - 539), n=17	0.73	333.5 (291 - 408.25), n=14	305 (291 - 337), n=15	0.45
Reaction time mistakes	5 (0.5 - 19)	3 (0.5 - 11)	0.39	2.5 (0 - 5.75)	1 (0 - 2)	0.20
Reaction time missing	1 (0 - 4)	0 (0 - 1)	0.43	0 (0 - 3)	0 (0 - 1)	0.72
SS-QoL Mobility	27.5 (26.25 - 30), n=12	25 (22.5 - 30), n=17	0.30	29 (23 - 30), n=13	28 (26 - 30), n=15	0.86
SS-QoL Energy	10 (6.5 - 12), n=12	6 (4 - 9.5), n=17	0.021	9 (6 - 11.5), n=13	7 (3 - 10), n=15	0.20
SS-QoL Upper extremity function	24 (21.5 - 25), n=12	22 (14.5 - 24.5), n=17	0.20	24 (23 - 25), n=13	22 (18 - 25), n=15	0.10
SS-QoL Work and productivity	14 (13 - 15), n=12	12 (9 - 13.5), n=17	0.048	15 (11.5 - 15), n=13	12 (11 - 14), n=15	0.16
SS-QoL Mood	21.5 (17 - 25), n=12	19 (13.5 - 23), n=17	0.17	23 (19 - 25), n=13	21 (13 - 25), n=15	0.32
SS-QoL Self-care	25 (21.25 - 25), n=12	22 (17.5 - 24.5), n=17	0.30	25 (22 - 25), n=13	24 (22 - 25), n=15	0.41
SS-QoL Social roles	17 (11.25 - 20.75), n=12	13 (7 - 19.5), n=17	0.15	20 (8.5 - 21.5), n=13	16 (10 - 22), n=15	1.00
SS-QoL Family roles	12 (9.5 - 15), n=12	11 (7 - 13), n=17	0.23	14 (10.5 - 15), n=13	12 (7 - 15), n=15	0.41
SS-QoL Vision	15 (14.25 - 15), n=12	15 (13 - 15), n=17	0.37	15 (14.5 - 15), n=13	15 (13 - 15), n=15	0.39
SS-QoL Language	25 (22.5 - 25), n=12	21 (17 - 24), n=17	0.006	25 (23 - 25), n=13	21 (18 - 25), n=15	0.037
SS-QoL Thinking	14 (10.25 - 15), n=12	10 (6 - 14.5), n=17	0.13	15 (11.5 - 15), n=13	10 (5 - 15), n=15	0.041
SS-QoL Personality	13 (11.25 - 15), n=12	12 (9 - 15), n=17	0.37	14 (8 - 15), n=13	11 (9 - 15), n=15	0.59

IQR; Inter-Quartile Range, MFI-20; Multidimensional Fatige Inventory; MOCA; Montreal Cognitive Assesment, SS-QoL; Stroke Specific Quality of Life