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CLINICAL ARTICLE

(–)-OSU6162 in the treatment of fatigue and other sequelae after aneurysmal subarachnoid hemorrhage: a double-blind, randomized, placebo-controlled study

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OBJECTIVE Fatigue after aneurysmal subarachnoid hemorrhage (aSAH) is common and usually long-lasting, and it has a considerable negative impact on health-related quality of life (HRQOL), social functioning, and the ability to return to work (RTW). No effective treatment exists. The dopaminergic regulator (−)-OSU6162 has shown promising results regarding the mitigation of fatigue in various neurological diseases, and therefore the authors aimed to investigate the efficacy of (−)-OSU6162 in alleviating fatigue and other sequelae after aSAH.

METHODS A double-blind, randomized, placebo-controlled, single-center trial was performed in which 96 participants with post-aSAH fatigue were administered 30–60 mg/day of (−)-OSU6162 or placebo over a period of 12 weeks. Efficacy was assessed using the Fatigue Severity Scale (FSS), the Mental Fatigue Scale (MFS), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI-II), the SF-36 questionnaire, and a neuropsychological test battery. Assessments were performed at baseline, after 1, 4, 8, and 12 weeks of treatment, and at follow-up, 8 weeks after treatment.

RESULTS The 96 participants with post-aSAH fatigue were randomized to treatment with (−)-OSU6162 (n = 49) or placebo (n = 47). The FSS, MFS, and BDI scores improved significantly in both groups after 12 weeks of treatment, whereas the BAI scores improved in the placebo group only. HRQOL improved significantly in the SF-36 domain "Vitality" in both groups. Neuropsychological test performances were within the normal range at baseline and not affected by treatment. The FSS score was distinctly improved in patients with complete RTW upon treatment with (−)-OSU6162. Concomitant use of antidepressants improved the efficacy of (−)-OSU6162 on the FSS score at week 1 beyond the placebo response, and correspondingly the use of beta- or calcium-channel blockers improved the (−)-OSU6162 efficacy beyond the placebo response in MFS scores at week 4 of treatment. There was a significant correlation between improvement in FSS, BAI, and BDI scores and the plasma concentration of (−)-OSU6162 at the dose of 60 mg/day. No serious adverse events were attributable to the treatment, but dizziness was reported more often in the (−)-OSU6162 group.

CONCLUSIONS Fatigue and other sequelae after aSAH were similarly alleviated by treatment with (−)-OSU6162 and placebo. (−)-OSU6162 improved fatigue, as measured with the FSS score, significantly in patients with complete RTW. There seemed to be synergetic effects of (−)-OSU6162 and medications interfering with dopaminergic pathways that should be explored further. The strong placebo response may be exploited in developing nonpharmacological treatment programs for post-aSAH fatigue.

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KEYWORDS aneurysmal subarachnoid hemorrhage; fatigue; (−)-OSU6162; clinical trial; neuropsychology; placebo; return to work; vascular disorders

ABBREVIATIONS AE = adverse event; aSAH = aneurysmal subarachnoid hemorrhage; ATC = Anatomical Therapeutic Chemical; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory II; CLVT-II = California Verbal Learning Test, Second Edition; CPT-III = Conners Continuous Performance, Third Edition; CWIT = Color-Word Interference Test; D-KEFS = Delis-Kaplan Executive Function System; ECG = electrocardiography; FSS = Fatigue Severity Scale; HRQOL = health-related quality of life; MFS = Mental Fatigue Scale; mRS = modified Rankin Scale; RTW = return to work; TBI = traumatic brain injury; WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition; 5-HT2A = 5-hydroxytryptamine 2A.

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Fatigue impedes long-term functional outcome after aneurysmal subarachnoid hemorrhage (aSAH).[1,2] Post-aSAH fatigue is often long-lasting or permanent and has a considerable negative impact on health-related quality of life (HRQOL), social functioning, and the ability to return to work (RTW).[1,3–6] Fatigue is present in 31%–90% of aSAH survivors and hence poses not only a personal, but also a socioeconomic problem, even in good-outcome aSAH.[1–3,5–7]

Post-aSAH fatigue often occurs together with emotional and cognitive problems, and this cluster of aSAH sequelae has been denoted post-aSAH syndrome.[4] Emotional symptoms like anxiety and depression can be treated medically, but this does not eradicate fatigue.[8,9] Despite the disabling nature of the post-aSAH syndrome, there is a remarkable lack of treatment and intervention research, with hitherto merely one pharmacological study from 1998 aiming at reducing post-aSAH fatigue.[10]

The underlying cause of central fatigue is not well understood, but imbalance of the neurotransmitters serotonin and, foremost, dopamine has been suggested.[11,12] Dopamine is a regulator of motivation and effortful behavior, and imbalance in the dopaminergic pathways has been linked to fatigue and cognitive dysfunction.[11] The serotonergic system is important for neuroplasticity, emotional responses, and sleep. (–)-OSU6162 is a monoaminergic stabilizer affecting both neurotransmitter systems by acting antagonistically at the D2 dopamine receptor and partially agonistically on the serotonergic 5-hydroxytryptamine 2A (5-HT2A) receptor.[13,14] Clinical trials investigating the effect of (–)-OSU6162 on fatigue and other sequelae after stroke and traumatic brain injury (TBI) have been promising, although not conclusive.[14–16] (–)-OSU6162 mitigated fatigue and improved mood and HRQOL in patients with chronic fatigue syndrome or multiple sclerosis in open-label studies.[17,18] The positive effect of (–)-OSU6162 was enhanced in patients with fatigue who were also treated with antidepressants and in those with low rates of RTW.[16,19] Reported toxicity studies of (–)-OSU6162 found increases in heart rate and prolongation of the QTc interval at high doses, whereas side effects in clinical studies were transient and mild, mainly consisting of nausea, dizziness, and changed appetite; i.e., (–)-OSU6162 has a favorable safety profile.[14,15,17,20]

To our knowledge the effect of (–)-OSU6162 on the post-aSAH syndrome has not been previously investigated. Therefore, in the present double-blind, randomized, placebo-controlled study we sought to explore the overall and subgroup efficacy of (–)-OSU6162 for treatment of fatigue, anxiety, depression, HRQOL, and cognitive problems in the chronic phase after aSAH.

Methods

This double-blind, randomized, single-center clinical trial was conducted at Oslo University Hospital, Norway, and has the EudraCT unique identifier 2016-004739-19 and ClinicalTrials.gov number NCT03209830. The national competent authority and regional ethics committee approved the study.

Patients

Adult patients (> 18 years old) in the chronic phase of aSAH (ictus > 12 months prior to inclusion) were eligible if they had a Fatigue Severity Scale (FSS)[21] mean score ≥ 4.0. Exclusion criteria were brain surgery within the last 12 months, active neurological disease (including epilepsy), current drug abuse, pathological electrocardiography (ECG) with QTc interval > 480 msec, significant blood test deviations, and pregnancy. Patients using antipsychotic medication, drugs capable of inhibiting or inducing hepatic enzyme metabolism, or medications with a narrow treatment window were not allowed into the study. Patients deemed cognitively too debilitated to consent to and/or perform the assessments, and those with language abilities too poor to understand the questionnaires were excluded.

All patients with aSAH between January 2012 and March 2018 were identified and phoned for an interview that included assessment of the FSS. Those with an FSS mean score ≥ 4 and without exclusion criteria were invited to a screening visit where they signed written informed consent. Female patients of childbearing potential agreed to use a highly efficient method of contraception. Male patients agreed to use condoms during and for 3 months after the end of the study.

Investigational Products

(–)-OSU6162 and the placebo were round, white, 15-mg-strength tablets with identical coating weighing 242 mg. (–)-OSU6162 tablets contained 15 mg of 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride in addition to the same inactive ingredients as the placebo (cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate).

Study Procedures

The study was conducted in accordance with Good Clinical Practice guidelines.[22] Figure 1 illustrates the timeline of study procedures. Questionnaires were answered by the participants electronically in Viedoc at home at their own pace, but within a predefined time window. We interviewed the patients at all points of assessment and noted adverse events (AEs) and changes in medication. Drug accountability was addressed at every visit.

The hospital's clinical trial unit generated a 1:1 randomization list that they sent to the drug producer and integrated into the electronic case report form in Viedoc. When the investigator pushed the randomization button in Viedoc, a locked randomization number appeared. Patients received the drug vial with their randomization number. Apart from the randomization number, all vials were identical, and thereby the double-blinding was kept when we randomized to (–)-OSU6162 or placebo for 12 weeks with an initial dosage of 30 mg/day (15 mg × 2). After at least 1 week of treatment, those with less than 1.5 points of improvement on the FSS mean score or without other convincing positive effects had their dose increased to 60 mg/day (30 mg × 2). Given some positive effect (but not full response) at week 1, the dosage increase could be postponed to week 4 or 8.

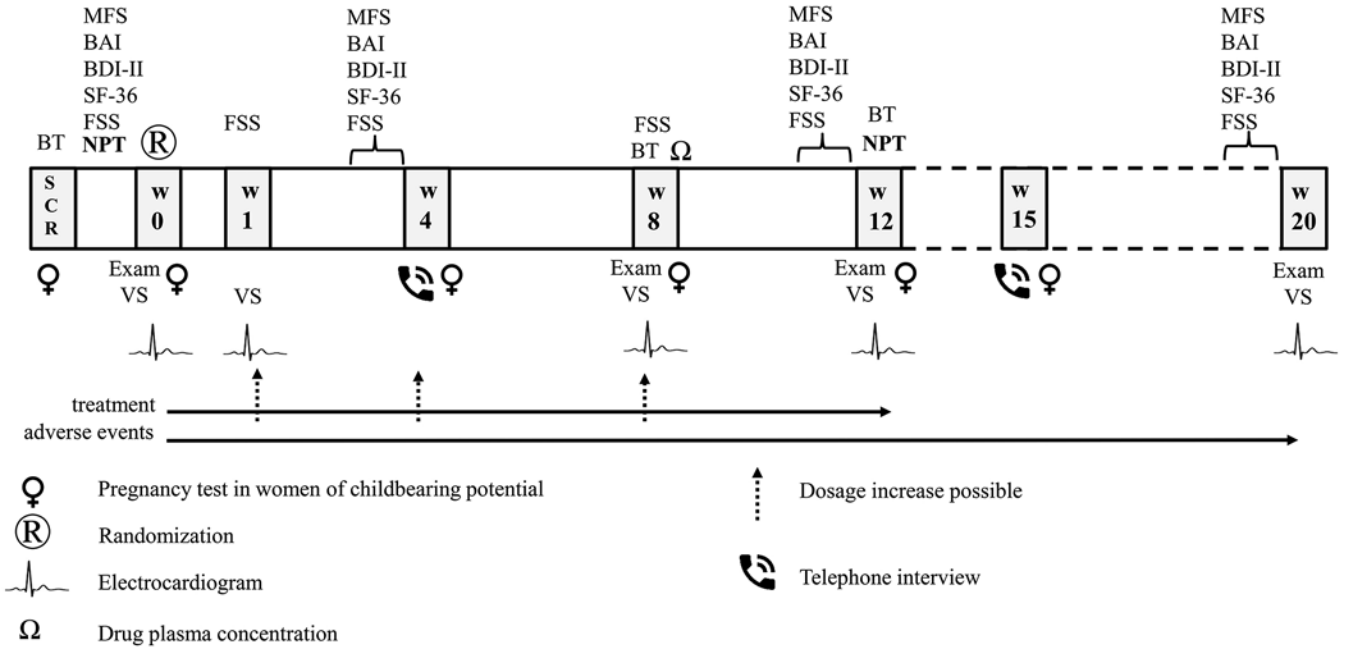

FIG. 1. Timeline of study procedures. Questionnaires: FSS, MFS, BAI, BDI-II, SF-36; BT = blood and urine tests; Exam = physical and neurological examination; NPT = neuropsychological test; SCR = screening; VS = vital signs; w = week; w20 = follow-up visit.

If not tolerated, 60 mg/day was reduced immediately to 30 mg/day.

In week 8, blood tests were drawn 60–120 minutes after drug intake for analysis of the drug plasma concentration. The plasma samples were stored at –80°C until analyzed as previously described.[23]

Measures

The primary outcome variable was FSS score,[21] which is based on a 9-item questionnaire measuring the severity of fatigue and its effect on a person's daily activities. Items are scored on a 7-point Likert scale and expressed as FSS mean score.

Fatigue after aSAH has been described as prevailingly mental fatigue,[1,24] and therefore we also used the Mental Fatigue Scale (MFS).[25] It consists of 15 items that relate to fatigue, sleep patterns, and affective and cognitive symptoms. Each item is linked to four statements that rank the severity between 0 and 3. Items 1–14 are summarized and a sum score ≥ 10.5 is suggestive of mental fatigue.[25]

Symptoms of anxiety and depression were assessed using the Beck Anxiety Inventory (BAI)[26] and the Beck Depression Inventory (BDI-II)[27] scores, respectively. HRQOL was evaluated with the SF-36[6,28] questionnaire. Results from the SF-36 were expressed using t-scores, where a value of 50 corresponds to the sex- and age-adjusted population mean.[29]

The neuropsychological domains of sensorimotor function, attention, psychomotor speed, verbal learning, verbal memory, and executive function were evaluated using the following tests: the Grooved Pegboard; the California Verbal Learning Test, Second Edition (CLVT-II); Conners Continuous Performance, Third Edition (CPT-III); the Digit Span from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV); the Trail Making Tests (1 through 5); and the Color-Word Interference Tests (CWITs) 1 through 4 from the Delis-Kaplan Executive Function System (D-KEFS). All tests were scored using published normal values, and raw scores were converted into z-scores, which allow comparison to the normal population, in which z-scores between 1.00 and –1.49 indicate mild impairment and scores between –1.50 and –2.00 indicate moderate impairment, whereas z-scores below –2.00 indicate neuropsychological deficit.

Statistics

Analysis was based on all randomized patients who took at least one dose of trial medication and had at least one assessment of primary efficacy. We used SPSS version 26 (IBM Corp.) and adopted a significance level of 5% (two-sided). Continuous data were presented as mean ± standard deviation (SD) if normally distributed, and as median with interquartile range (IQR) if not normally distributed. We presented categorical data as percentages and analyzed differences between groups with chi-square tests. The changes from baseline to assessment points were analyzed with the paired Student t-test or Wilcoxon paired sample test as appropriate. We compared treatment groups with the independent-samples t-test or Mann-Whitney U-test, depending on the distribution of observed differences. Based on published data on FSS scores after aSAH,[7] an alpha level of 0.05, 90% power, and a sample size of 42 patients in each group were needed to detect a difference of 1.0 in FSS mean score.

Results

Patients

Figure 2 shows the flowchart of eligible and included

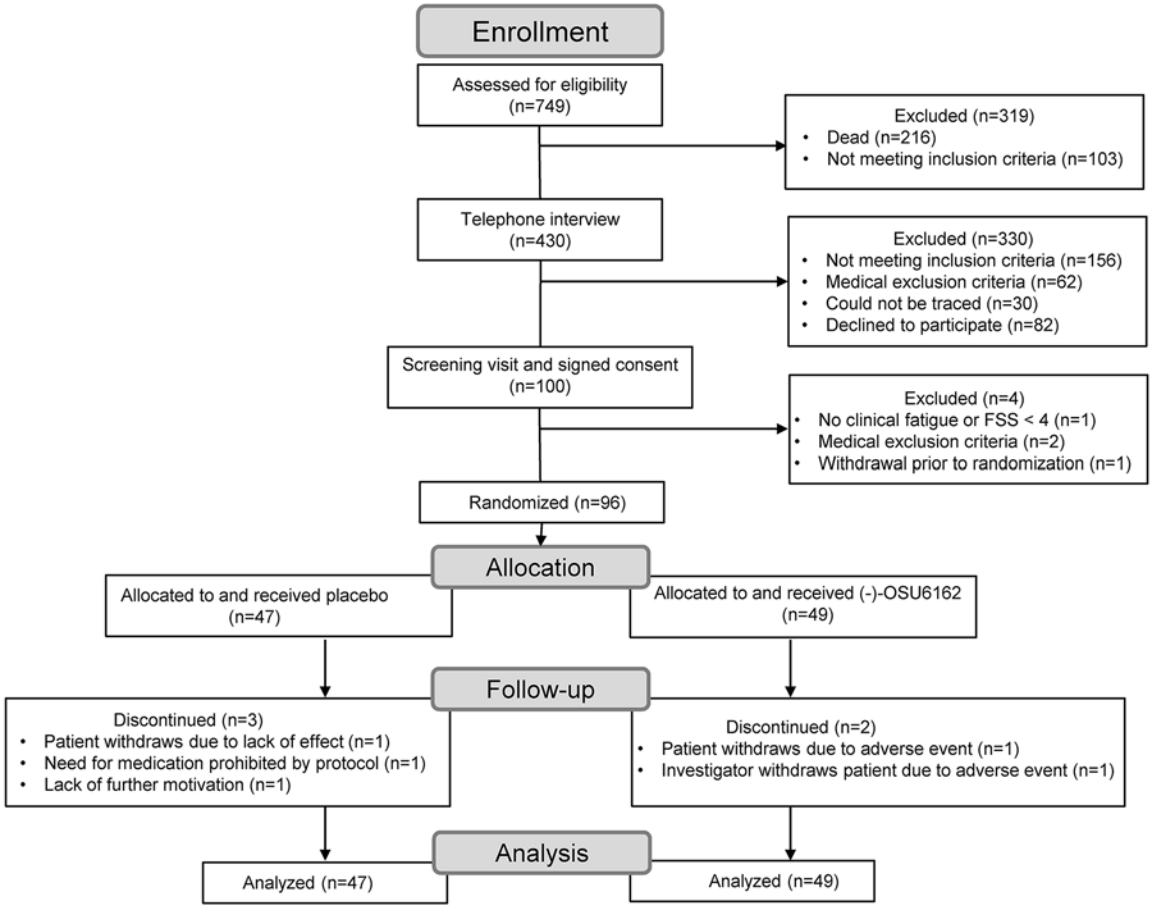

FIG. 2. Flowchart of eligible and included patients along with randomization to treatment with either (−)-OSU6162 or placebo.

patients. We randomized 96 participants to treatment with (–)-OSU6162 (n = 49) or placebo (n = 47).

There were no significant differences in the use of concomitant medications and comorbidity between treatment groups apart from patients in the (–)-OSU6162 group having more frequent neurological problems, which mainly consisted of chronic headaches (63% vs 40%, p = 0.025). None of the participants had significant neurological deficits and all had good outcome, with modified Rankin Scale[30] (mRS) scores of 0–2: 0 (n = 5), 1 (n = 68), 2 (n = 23).

The treatment groups were similar apart from frontal cerebral infarctions being more frequent in the (–)-OSU6162 group (Table 1). Both treatment groups had scores indicating clinical fatigue on FSS and MFS, and they showed similar values for depression and anxiety indicating mild to moderate affective symptoms. The HRQOL domains general health, vitality, and social functioning were reduced to below 1 SD, whereas the other domains were within the normal range in both groups. Neuropsychological test performance fell within normal values in all domains and subtests (Table 1, Supplementary Table 1).

Dosages

The fractions of patients taking medication at a dosage of 60 mg/day at weeks 4 and 8 were 63.3% and 66% in the (–)-OSU6162 group and 59.6% and 75% in the placebo group (p = 0.710 and p = 0.345 between groups), respectively. Dose reduction (16.3%) and study withdrawal due to side effects (4.1%) occurred more often in the (–)-OSU6162 group than the placebo group, in which there was a rate of 6.4% for dose reduction and no withdrawals due to side effects (p = 0.045).

Efficacy

Figure 3 shows the percentage change from baseline to 12 weeks of treatment with (–)-OSU6162 (dark columns) or placebo (white columns) for all measurements.

Effect of Treatment on Fatigue

The FSS mean score improved significantly from baseline to every point of assessment in both treatment groups (Fig. 4A, upper panel), but remained well below a decrease of 1.5 points (considered clinically significant). The improvement was larger in the (–)-OSU6162 group except at week 12; however, this difference did not reach statistical significance. At week 12, 21.3% in the (–)-OSU6162 group and 20.5% in the placebo group no longer scored for clinical fatigue (FSS mean score < 4, p = 0.923). When analyzing the 9 individual items of the FSS, item 7 ("Fatigue

TABLE 1. Baseline demographic and clinical characteristics for each treatment group

	(−)−OSU6162 (n = 49)	Placebo (n = 47)	p Value
Demographics, radiology, & vital signs			
Age, yrs	54.4 ± 9.5	56.2 ± 10.60	0.388
Time from ictus to inclusion, yrs	2.33 (1.58–4.67)	1.75 (1.17–3.58)	0.069
Female/male	35:14	30:17	0.426
BMI, kg/m^2	28.94 ± 5.48	29.73 ± 7.38	0.552
Cerebral infarction	42.9%	27.7%	0.120
Frontal cerebral infarction	26.5%	10.6%	0.046
Systolic blood pressure	131.2 ± 14.2	137.3 ± 15.8	0.050
Diastolic blood pressure	82.5 ± 8.1	85.6 ± 9.3	0.081
Heart rate	68.3 ± 9.7	70.5 ± 12.2	0.345
QTc interval	421.8 ± 19.1	422.4 ± 17.3	0.866
RTW			
No paid work at ictus	7 (14.3%)	11 (23.4%)	0.253
No RTW at inclusion	23 (46.9%)	20 (42.6%)	0.666
Partial RTW at inclusion	15 (30.6%)	10 (21.3%)	0.297
Complete RTW at inclusion	4 (8.2%)	6 (12.8%)	0.461
Concomitant medication in subgroup analysis			
Antidepressants	13 (26.5%)	15 (31.9%)	0.562
Beta- or calcium-channel blockers	14 (28.6%)	15 (31.9%)	0.721
Questionnaires			
FSS mean score[21]	6.04 ± 0.66	5.91 ± 0.90	0.440
MFS sum score[25]	17.9 ± 4.7	18.4 ± 6.4	0.699
BAI sum score[26]	7.9 ± 6.3	9.9 ± 7.7	0.163
BDI-II sum score[27]	14.98 ± 8.11	17.53 ± 9.30	0.156
SF-36, t-scores[28]			
Physical function	43.3 (37.2–52.8)	43.3 (34.5–50.6)	0.502
Physical role function	38.6 (32.4–47.1)	36.5 (32.4–42.4)	0.985
Bodily pain	44.7 (37.4–53.2)	43.7 (37.8–53.3)	0.533
General health	39.9 (36.5–44.4)	40.7 (38.3–45.1)	0.484
Vitality	37.3 (30.7–43.0)	37.3 (27.1–42.6)	0.575
Social function	40.0 (35.2–44.4)	36.4 (27.8–42.2)	0.065
Emotional role function	53.8 (31.2–54.8)	47.0 (30.0–54.8)	0.738
Mental health	44.8 (34.9–52.2)	46.9 (34.4–52.2)	0.493
Neuropsychological tests, z-scores			
Sensorimotor function	−0.65 (−1.35–0.00)	−0.50 (−1.10–0.00)	0.313
Attention	0.00 (−0.65–60)	0.00 (−0.68–0.40)	0.394
Psychomotor speed	0.00 (−0.65–0.65)	0.00 (−0.65–0.65)	0.538
Verbal learning	−0.80 (−1.50–0.00)	−0.50 (−1.00–0.00)	0.101
Verbal memory	0.00 (−1.00–0.50)	0.00 (−1.00–0.50)	0.661
Executive function	0.00 (−0.65–0.65)	0.35 (−0.65–0.65)	0.434

Values are presented as mean ± SD or median (IQR); p values are presented for differences between treatment groups.

interferes with carrying out certain duties and responsibilities") was improved more at week 4 in the (–)-OSU6162 group than in the placebo group (0.45- vs 0.09-point improvement, p = 0.039).

Subgroup analysis of concomitant medication categories within the Anatomical Therapeutic Chemical (ATC) classification system revealed that patients using antidepressants had improved efficacy of (–)-OSU6162 that exceeded the improvement in patients using placebo on the FSS mean score at week 1 (p = 0.047), week 12 (p = 0.049), and at follow-up (p = 0.049; Fig. 4A, middle panel). The efficacy of (–)-OSU6162 was also higher in the subgroup with concomitant use of beta- or calcium-channel blockers but did not exceed the efficacy seen in the placebo group (Fig. 4A, lower panel).

Subgroup analysis of RTW stratified into groups as dis-

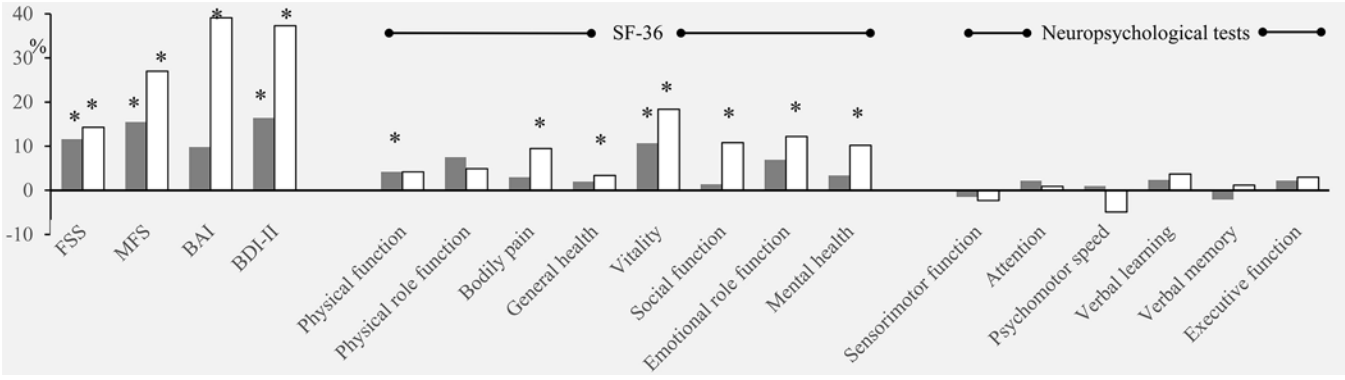

FIG. 3. Overview of percentage change from baseline to 12 weeks of treatment with (−)-OSU6162 (*dark columns*) or placebo (*white columns*) for the questionnaires FSS, MFS, BAI, BDI-II, the eight SF-36 domains, and the six domains of neuropsychological test performance. Improvement is shown as positive change and worsening as negative change. *p < 0.05.

played in Table 1 revealed a positive treatment effect of (–)-OSU6162 over placebo in those with complete RTW on FSS mean score at weeks 4, 8, and 12 (p = 0.049, p = 0.005, and p = 0.005; Fig. 5).

The MFS sum score improved (decreased) from baseline to weeks 4, 12, and follow-up in both treatment groups (Fig. 4B, upper panel). The fraction of clinically significant fatigue on the MFS (≥ 10.5 points) decreased from 93.6% at baseline to 75% at week 12 in the placebo group and from 93.9% to 80.9% in the (–)-OSU6162 group, respectively (p = 0.501). Some individual MFS items improved more in the placebo group: item 6 ("Memory problems"), at week 4 (0.227 vs 0.010 points, p = 0.028); and at week 12, item 3 ("Mental fatigue," 0.409 vs 0.170 points, p = 0.026) and item 11 ("Sensitivity for light," 0.205 vs –0.032 points, p = 0.043).

The improvement in MFS sum score was higher in patients treated with (–)-OSU6162 and concomitant use of antidepressants (Fig. 4B, middle panel) as well as concomitant use of beta- or calcium-channel blockers, exceeding

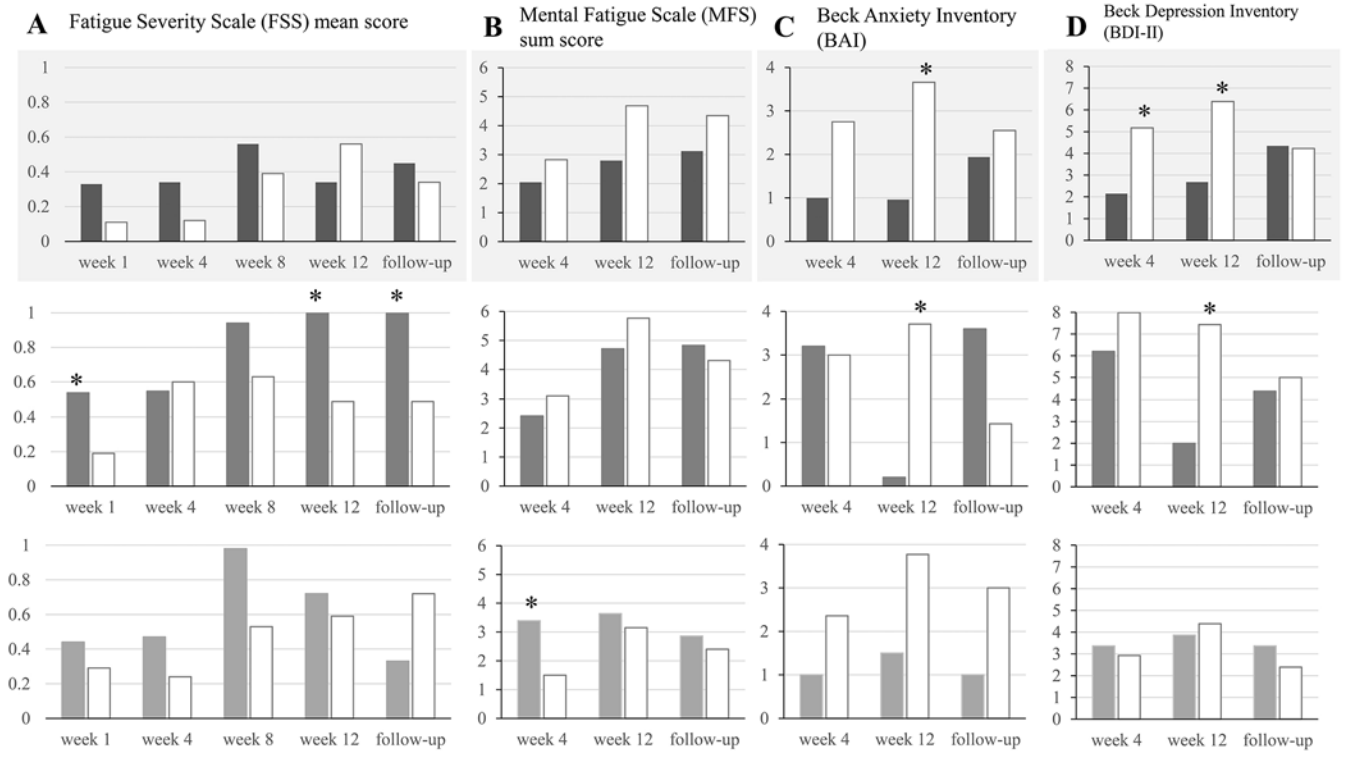

FIG. 4. Difference in points from baseline to the various times of assessment of the FSS mean score (**A**), MFS sum score (**B**), BAI score (**C**), and BDI-II score (**D**). The *upper panel* shows differences for all patients within treatment arms of (−)-OSU6162 (*dark columns*) and placebo (*white columns*). Subgroup analysis of patients within each treatment arm with concomitant use of antidepressants (*middle panel*) and patients with concomitant use of beta- or calcium-channel blocking agents (*lower panel*). *p < 0.05 for difference between treatment groups.

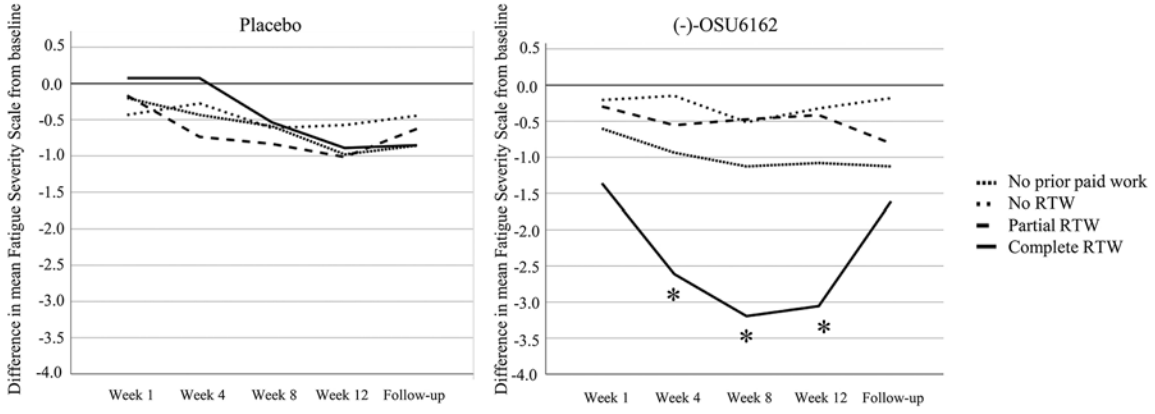

FIG. 5. Change in FSS mean score at 1, 4, 8, and 12 weeks of treatment with (−)-OSU6162 (*right*) or placebo (*left*) and at follow-up. Stratification into subgroups of those who had or did not have paid work at the time of ictus. Those who had paid work were further divided into those with no, partial, or complete RTW at entry into the study. *p < 0.05 for differences between treatment groups.

the efficacy of placebo at week 4 in the latter subgroup (Fig. 4B, lower panel). We found no significant group differences for the MFS in relation to RTW.

In the (–)-OSU6162 group, patients without frontal cerebral infarctions showed gradual improvement in FSS and MFS scores during treatment, whereas in patients with frontal infarctions the scores declined between weeks 4 and 12 of treatment (FSS, p = 0.045; MFS, p = 0.029). Within the placebo group, treatment responses measured with the FSS and MFS were similar among those with and those without frontal cerebral infarctions.

Effect of Treatment on Anxiety, Depression, and HRQOL

BAI scores improved more at week 12 and BDI-II scores at weeks 4 and 12 in the placebo group than in the (–)-OSU6162 group (Fig. 4C and D, upper panel).

Compared with patients not using antidepressants, patients with concomitant use of antidepressants showed improved efficacy of (–)-OSU6162 based on scores in the BAI (p = 0.024) and BDI-II (p = 0.012) in week 4. Still, combined use of (–)-OSU6162 and antidepressants was not superior to the efficacy of placebo at week 4 and clearly inferior to placebo at week 12 (Fig. 4C and D, middle panel). No significant treatment group differences were seen in the subgroup of patients using beta- or calcium-channel blockers (Fig. 4B and C, lower panel).

As Fig. 3 shows, HRQOL scores improved from baseline to week 12 in six of the HRQOL domains in the placebo group, but in merely two domains in the (–)-OSU6162 group. Vitality had the clearest improvement in both groups. Supplementary Fig. 1 shows the median HRQOL t-scores at all assessment points for all eight domains of the SF-36. There were no significant differences between treatment groups or subgroups of concomitant medication.

Effect of Treatment on Neuropsychological Performance

There were no significant changes in neuropsychological performance within the six domains after 12 weeks of treatment (Fig. 3 and Supplementary Table 1). In one subtest of executive function (D-KEFS, CWIT 4) scores had improved more in those treated with (–)-OSU6162, whereas in one subtest of psychomotor speed (D-KEFS, CWIT 1) scores had improved more after treatment with placebo. However, scores for both these subtests were well within the normal range at baseline.

Drug Plasma Concentration

Samples were drawn for measurement of (–)-OSU6162 plasma concentrations at a mean of 74 minutes after drug intake and results varied between 0.125 and 0.870 μM. Plasma concentration was not related to BMI (Pearson's correlation r = –0.015, p = 0.938) or weight (r = –0.109, p = 0.497). When stratified according to dosage, there was a significant correlation between decrease in FSS mean score and plasma concentration in those using 60 mg/day (Fig. 6, upper right; Pearson's r = –0.561, p = 0.002). A similar trend was seen for the decrease in MFS sum score (Fig. 6, lower right). We found no significant relation between drug concentration and efficacy in those using 30 mg/day (Fig. 6, left). The decrease in BAI and BDI-II scores was also correlated to plasma concentration in those using 60 mg/day (r = –0.438, p = 0.020; and r = –0.422, p = 0.025).

Safety

There were no significant changes in heart rate, weight, or QTc interval throughout the study in either group. Systolic and diastolic blood pressure decreased to within 5.0 mm Hg from baseline to week 12 in the placebo group but remained unchanged in the (–)-OSU6162 group. In the (–)-OSU6162 group, prolactin increased by 29.5% (2.2%–69.6%) (p = 0.002) at week 8 and 30.3% (1.1%–54.4%) (p = 0.026) at week 12. Since prolactin is a reliable biomarker for D2 occupancy, the observed increase documents that D2 antagonism by (–)-OSU6162 actually did occur.[20] In the subgroup of those with frontal infarction, the prolactin increase was almost absent (4.3% vs 42.1% in those without frontal infarctions, p = 0.021). There were no other significant changes in blood tests in either group.

Dizziness was reported more often in the (–)-OSU6162 group (24.5% vs 6.4%, p = 0.015), whereas dermatological AEs were more frequent in the placebo group (31.9% vs

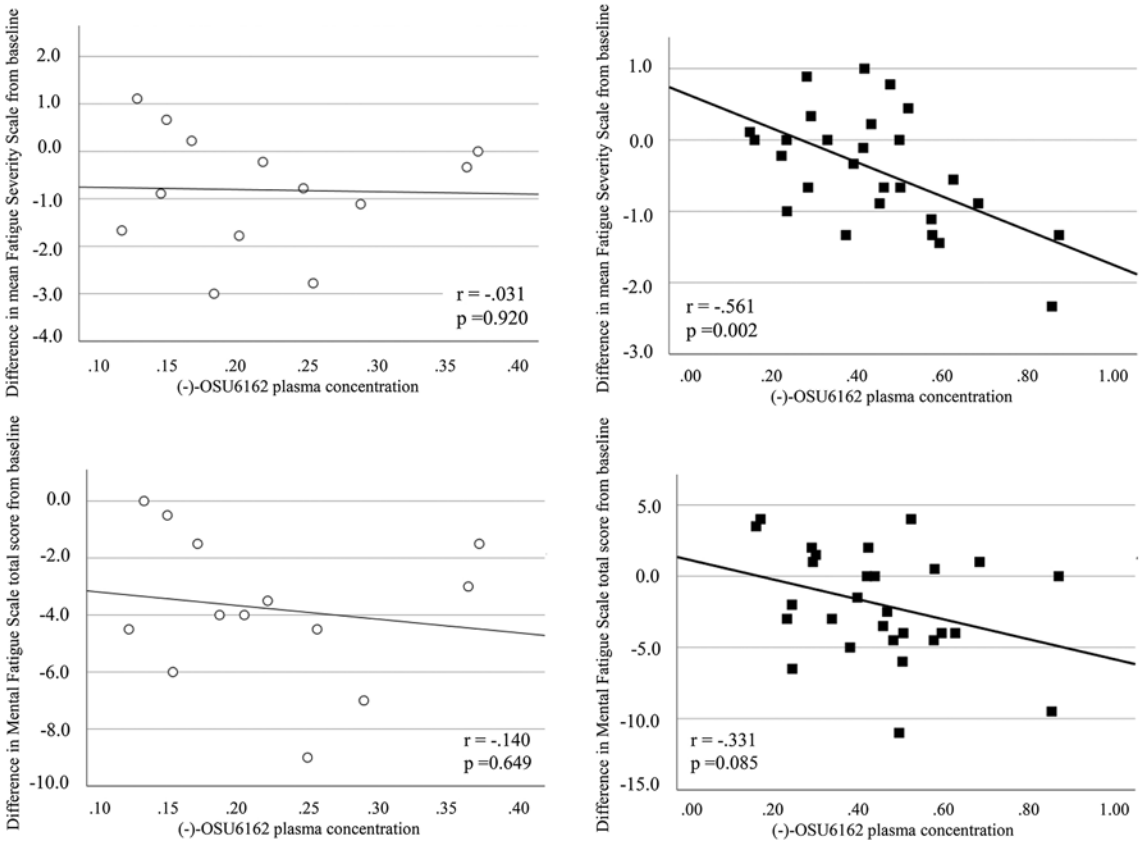

FIG. 6. Plasma concentration of (−)-OSU6162 in relation to decrease in FSS mean score (*upper*) and MFS sum score (*lower*) at week 8 stratified into study participants using 30 mg/day (15 mg × 2, *white circles, left*) and those using 60 mg/day (30 mg × 2, *black squares, right*). Pearson's correlation, 2-tailed p values.

12.2%, p = 0.02). Supplementary Table 2 provides a comprehensive overview of AEs in both groups.

The investigator withdrew 1 patient after 4 weeks of treatment with 30 mg/day of (–)-OSU6162 due to clinically significant low cortisol. One patient withdrew from the study due to feeling detached and drugged after increasing (–)-OSU6162 to 60 mg/day. No other severe treatment-related AEs occurred.

Discussion

The present study showed similar alleviation of fatigue during and after treatment with (–)-OSU6162 and placebo apart from in those with complete RTW who improved significantly on the FSS mean score upon treatment with (–)-OSU6162. The placebo response after 12 weeks of treatment was stronger than the effect of (–)-OSU6162 on anxiety (BAI), depressive symptoms (BDI-II), and HRQOL. Neuropsychological test performances were within the normal range at baseline and unaffected by treatment. The use of antidepressants improved the efficacy of (–)-OSU6162, as indicated by the FSS mean score, beyond the placebo response after 1 week of treatment and correspondingly, the use of beta- or calcium-channel blockers improved the (–)-OSU6162 efficacy beyond the placebo response in MFS at week 4 of treatment. There was a significant correlation between improvement in FSS, BAI, and BDI-II scores and (–)-OSU6162 plasma concentration in those using 60 mg/day.

(−)-OSU6162 in the Treatment of Neurological Conditions

The efficacy of (–)-OSU6162 has been investigated in various neurological conditions. In parallel to the present study, patients with fatigue after TBI showed improvements in FSS and MFS upon treatment with (–)-OSU6162 and placebo, whereas neuropsychological performance improved in both their treatment groups.[15] The latter is probably due to the TBI cohort having more neuropsychological deficits than our patients. (–)-OSU6162 alleviated fatigue similarly to placebo as measured with the MFS in patients with myalgic encephalomyelitis/chronic fatigue syndrome.[19] In the present study, we saw less effect of (–)-OSU6162 when evaluating fatigue with the MFS than with the FSS, so that the study of Nilsson et al.[19] may have found larger differences if another tool to measure fatigue had been used. Likewise, Nilsson et al.[16] found no overall effect on the MFS scores in their 30 patients with TBI or stroke. In a similar study with higher dosages of up to 90 mg/day, (–)-OSU6162 reduced the MFS sum score more than placebo.[14] Similarly higher dosages were used in a placebo-controlled crossover study in 12 patients with Huntington's disease that found a positive effect of (–)-OSU6162 on the SF-36 vitality domain and the BDI score.[31] This corrobo-

rates our study, albeit we observed similar or larger improvements in the placebo group. We increased the dosage from 30 to 60 mg/day if no sufficient treatment response was observed in our study. Hence, fatigue decreased in some patients at 30 mg/day. However, we saw a positive correlation of (–)-OSU6162 plasma concentration and improvement in FSS, MFS, BAI, and BDI-II only at dosages of 60 mg/day. Plasma concentrations were independent of body weight, indicating that individual pharmacokinetics are decisive for (–)-OSU6162 plasma concentration.

So far, to our knowledge, no other studies have investigated the effect of (–)-OSU6162 in patients with post-aSAH fatigue. Nevertheless, the aSAH group shares pathophysiological similarities with both stroke and TBI patients, so that similar results can be anticipated.

Efficacy of (−)-OSU6162 in Subgroups

Even though most studies failed to demonstrate efficacy of (–)-OSU6162 over placebo, several subgroups with boosted (–)-OSU6162 responses have been identified. In parallel with our findings, concomitant use of antidepressant drugs enhanced the efficacy of (–)-OSU6162.[19] The only antidepressant medications allowed in our study were selective serotonin reuptake inhibitors (SSRIs). (–)-OSU6162 exerts a stabilizing effect on serotonergic neuronal circuits, acting as a partial 5-HT2A agonist.[31] Blockade of the 5-HT2A receptor has been shown to augment the antidepressant effect of SSRIs.[32] In addition to interaction on the serotonergic pathway, there may be interactions with (–)-OSU6162 on the dopaminergic pathway: SSRIs increase endogenous dopamine concentrations, thereby causing a decrease in striatal D2 receptor availability,[33] i.e., the main site of action for (–)-OSU6162, which is a D2 antagonist mainly acting at the presynaptic site. These mechanisms may explain the larger improvement in FSS during concomitant treatment with (–)-OSU6162 and SSRIs.

We also observed enhanced efficacy of (–)-OSU6162 with concomitant use of beta- or calcium-channel blockers. Beta-blockers pass the blood-brain barrier and interact with the D2 receptor in a presynaptic mode of action similar to (–)-OSU6162.[34] Likewise, calcium-channel blockers reduce the striatal D2 receptor binding potential by 14%–63% in humans; an effect that may be observed up to several months after discontinuation of the calcium-channel blocker.[35] Such long-lasting effects may explain why enhanced (–)-OSU6162 responses in these two pharmacological subgroups were observed at follow-up in the present study. (–)-OSU6162 is a regulator/normalizer of dopaminergic influence on striatal neurons without changing the net output.[36] Its effect is therefore dopaminergic tone–dependent.[36] One may therefore assume that the efficacy of (–)-OSU6162 varies between individuals, dependent on their dopaminergic tone, and that some concomitant medications can cause a shift toward a more optimal mode of action for (–)-OSU6162. Such possible synergetic effects should be explored further.

Our subgroup with complete RTW showed a striking alleviation of fatigue as indicated by FSS mean scores upon treatment with (–)-OSU6162. Nilsson et al.[16] found that patients with the highest levels of sick leave showed larger decreases in MFS sum scores upon (–)-OSU6162 treatment. Their main finding was that (–)-OSU6162 leads to an increase in activity levels as measured with the Frenchay Activity Index.[16] Unlike the MFS, the FSS measures the effect of fatigue on daily life, so that increased activity levels may become more obvious in those with complete RTW who strain their energy levels the most. This could also explain that we found FSS item 7 ("Fatigue interferes with carrying out certain duties and responsibilities") to be most improved in those treated with (–)-OSU6162.

Placebo Effect

In parallel to studies investigating the effect of (–)-OSU6162 and placebo in patients with fatigue after TBI or patients with chronic fatigue syndrome, our study showed a remarkably pronounced placebo response within all the examined aspects of post-aSAH sequelae.[15,19] Patients choosing to participate in a clinical trial like ours are not neutral. They enter the study with hope and expectations and are being submitted to verbal suggestion, study routines (rituals), and rewards like attention and feelings of safety, thereby decreasing uncertainty and anxiety (which in turn can lead to perceived improvement). All these are powerful ingredients with respect to creating the psychosocial context effect that constitutes the placebo response.[37] These findings also nourish hope that cognitive treatment protocols exploiting the placebo effect could be effective in patients with post-aSAH fatigue. Positive expectations trigger the reward circuit, and placebos are capable of activating the mesolimbic dopaminergic system.[37] Placebo administration leads to considerable striatal dopamine release in the magnitude of responses seen after amphetamine in subjects that expect positive effects/reward.[38] Placebo and (–)-OSU6162 hence affect the same dopaminergic pathway and may cause similar modulations of dopaminergic tone and neurobiological effects.[19] We assume that the placebo response was similar in both our treatment groups. Whereas the placebo group gradually improved throughout the treatment period, we saw a decline in response beyond 4 weeks of treatment in the (–)-OSU6162 group. This either may indicate a shift away from the optimal point on the inverted U-shaped dose-response curve of (–)-OSU6162 or may be attributable to the patients with frontal infarctions who displayed a decline after 4 weeks of treatment with (–)-OSU6162. The latter is supported by the low prolactin increase in those with frontal infarctions indicating a low antagonistic D2 occupancy by (–)-OSU6162. Structural damage along the mesolimbic pathway may hence possibly interfere with the efficacy of (–)-OSU6162.

Study Strengths and Limitations

Our study is hitherto the largest clinical trial involving (–)-OSU6162, and to our knowledge the first to study the effect of this substance on sequelae after aSAH. Nevertheless, the total amount of participants is moderate or low in subgroups and larger numbers may have yielded clearer differences between treatment groups. Since our aSAH cohort consisted exclusively of good-outcome patients, we anticipate a ceiling effect for neuropsychological test performance. Inclusion of more disabled patients

could have produced different results. We included patients over a wide time frame from the ictus, which may have introduced uncertainties regarding the etiology of fatigue. Notwithstanding, the remarkably stable persistence of post-aSAH fatigue over many years rendered our time frame into a strength.[3,39] Our treatment period of 12 weeks is the longest reported, and reduced efficacy beyond 4 weeks of treatment would not have been detected by the earlier studies administering (–)-OSU6162 for merely 1–4 weeks.[14–16,19,31]

Conclusions

Fatigue and other sequelae after aSAH were similarly alleviated by treatment with (–)-OSU6162 and placebo. (–)-OSU6162 improved fatigue significantly in patients with complete RTW as measured with the FSS. There seem to be synergetic effects of (–)-OSU6162 and medications interfering with dopaminergic pathways that should be explored further. The strong placebo response may be exploited in developing nonpharmacological treatment programs.

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References

1. Buunk AM, Groen RJM, Wijbenga RA, Ziengs AL, Metzemaekers JDM, van Dijk JMC, Spikman JM. Mental versus physical fatigue after subarachnoid hemorrhage: differential associations with outcome. *Eur J Neurol*. 2018;25(11):1313-e113.
2. Samuelsson J, Jakobsson H, Rentzos A, Jakola AS, Nilsson D. Neurological outcome, mental fatigue, and occurrence of aneurysms >15 years after aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2021;151:e122-e127.
3. Western E, Sorteberg A, Brunborg C, Nordenmark TH. Prevalence and predictors of fatigue after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2020;162(12):3107-3116.
4. Haug Nordenmark T, Karic T, Røe C, Sorteberg W, Sorteberg A. The post-aSAH syndrome: a self-reported cluster of symptoms in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2019;132(5):1556-1565.
5. Passier PE, Post MW, van Zandvoort MJ, Rinkel GJ, Lindeman E, Visser-Meily JM. Predicting fatigue 1 year after aneurysmal subarachnoid hemorrhage. *J Neurol*. 2011;258(6):1091-1097.
6. Powell J, Kitchen N, Heslin J, Greenwood R. Psychosocial outcomes at 18 months after good neurological recovery from aneurysmal subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1119-1124.
7. Kutlubaev MA, Barugh AJ, Mead GE. Fatigue after subarachnoid haemorrhage: a systematic review. *J Psychosom Res*. 2012;72(4):305-310.
8. Huttunen J, Lindgren A, Kurki MI, Huttunen T, Frösen J, von Und Zu Fraunberg M, et al. Antidepressant use after aneurysmal subarachnoid hemorrhage: a population-based case-control study. *Stroke*. 2016;47(9):2242-2248.
9. Morris PG, Wilson JT, Dunn L. Anxiety and depression after spontaneous subarachnoid hemorrhage. *Neurosurgery*. 2004;54(1):47-54.
10. Ogden JA, Mee EW, Utley T. Too little, too late: does tirilazad mesylate reduce fatigue after subarachnoid hemorrhage? *Neurosurgery*. 1998;43(4):782-787.
11. Dobryakova E, Genova HM, DeLuca J, Wylie GR. The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders. *Front Neurol*. 2015;6:52.
12. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet*. 2004;363(9413):978-988.
13. Carlsson ML, Burstein ES, Kloberg A, Hansson S, Schedwin A, Nilsson M, et al. I. In vivo evidence for partial agonist effects of (-)-OSU6162 and (+)-OSU6162 on 5-HT2A serotonin receptors. *J Neural Transm (Vienna)*. 2011;118(11):1511-1522.
14. Johansson B, Carlsson A, Carlsson ML, Karlsson M, Nilsson MK, Nordquist-Brandt E, Rönnbäck L. Placebo-controlled cross-over study of the monoaminergic stabiliser (-)-OSU6162 in mental fatigue following stroke or traumatic brain injury. *Acta Neuropsychiatr*. 2012;24(5):266-274.
15. Berginström N, Nordström P, Schuit R, Nordström A. The effects of (-)-OSU6162 on chronic fatigue in patients with traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil*. 2017;32(2):E46-E54.
16. Nilsson MKL, Johansson B, Carlsson ML, Schuit RC, Rönnbäck L. Effect of the monoaminergic stabiliser (-)-OSU6162 on mental fatigue following stroke or traumatic brain injury. *Acta Neuropsychiatr*. 2020;32(6):303-312.
17. Haghighi S, Forsmark S, Zachrisson O, Carlsson A, Nilsson MKL, Carlsson ML, et al. Open-label study with the monoamine stabilizer (-)-OSU6162 in myalgic encephalomyelitis/chronic fatigue syndrome. *Brain Behav*. 2021;11(4):e02040.
18. Haghighi S, Forsmark S, Carlsson A, Nilsson MKL, Carlsson ML, Schuit RC, Gottfries CG. Open study with (-)-OSU6162 in multiple sclerosis-related fatigue. *Acta Neurol Scand*. 2018;138(6):482-489.
19. Nilsson MKL, Zachrisson O, Gottfries CG, Matousek M, Peilot B, Forsmark S, et al. A randomised controlled trial of the monoaminergic stabiliser (-)-OSU6162 in treatment of myalgic encephalomyelitis/chronic fatigue syndrome. *Acta Neuropsychiatr*. 2018;30(3):148-157.
20. Rodríguez CA, Azie NE, Adams G, Donaldson K, Francom SF, Staton BA, Bombardt PA. Single oral dose safety, tolerability, and pharmacokinetics of PNU-96391 in healthy volunteers. *J Clin Pharmacol*. 2004;44(3):276-283.
21. Lerdal A, Wahl A, Rustøen T, Hanestad BR, Moum T. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J Public Health*. 2005;33(2):123-130.
22. European Medicines Agency. Good Clinical Practice (GCP). Accessed August 6, 2021. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice
23. Tolboom N, Berendse HW, Leysen JE, Yaqub M, van Berckel BN, Schuit RC, et al. The dopamine stabilizer (-)-OSU6162 occupies a subpopulation of striatal dopamine D2/D3 receptors: an [(11)C]raclopride PET study in healthy human subjects. *Neuropsychopharmacology*. 2015;40(2):472-479.
24. Sörbo A, Eiving I, Löwhagen Hendén P, Naredi S, Ljungqvist J, Odenstedt Hergès H. Mental fatigue assessment may add information after aneurysmal subarachnoid hemorrhage. *Brain Behav*. 2019;9(7):e01303.
25. Johansson B, Starmark A, Berglund P, Rödholm M, Rönnbäck L. A self-assessment questionnaire for mental fatigue and related symptoms after neurological disorders and injuries. *Brain Inj*. 2010;24(1):2-12.
26. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56(6):893-897.
27. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory Manual*. 2nd ed. Psychological Corporation; 1996.
28. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

29. Garratt AM, Stavem K. Measurement properties and normative data for the Norwegian SF-36: results from a general population survey. *Health Qual Life Outcomes*. 2017;15(1):51.
30. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19(12):1497-1500.
31. Kloberg A, Constantinescu R, Nilsson MK, Carlsson ML, Carlsson A, Wahlström J, Haghighi S. Tolerability and efficacy of the monoaminergic stabilizer (-)-OSU6162 (PNU-96391A) in Huntington's disease: a double-blind cross-over study. *Acta Neuropsychiatr*. 2014;26(5):298-306.
32. Celada P, Puig M, Amargós-Bosch M, Adell A, Artigas F. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. *J Psychiatry Neurosci*. 2004;29(4):252-265.
33. Smith GS, Ma Y, Dhawan V, Chaly T, Eidelberg D. Selective serotonin reuptake inhibitor (SSRI) modulation of striatal dopamine measured with [11C]-raclopride and positron emission tomography. *Synapse*. 2009;63(1):1-6.
34. Bhide N, Lindenbach D, Barnum CJ, George JA, Surrena MA, Bishop C. Effects of the beta-adrenergic receptor antagonist Propranolol on dyskinesia and L-DOPA-induced striatal DA efflux in the hemi-parkinsonian rat. *J Neurochem*. 2015;134(2):222-232.
35. Brücke T, Wöber C, Podreka I, Wöber-Bingöl C, Asenbaum S, Aull S, et al. D2 receptor blockade by flunarizine and cinnarizine explains extrapyramidal side effects. A SPECT study. *J Cereb Blood Flow Metab*. 1995;15(3):513-518.
36. Tedroff J, Torstenson R, Hartvig P, Sonesson C, Waters N, Carlsson A, et al. Effects of the substituted (S)-3-phenylpiperidine (-)-OSU6162 on PET measurements in subhuman primates: evidence for tone-dependent normalization of striatal dopaminergic activity. *Synapse*. 1998;28(4):280-287.
37. Benedetti F, Carlino E, Pollo A. How placebos change the patient's brain. *Neuropsychopharmacology*. 2011;36(1):339-354.
38. de la Fuente-Fernández R, Phillips AG, Zamburlini M, Sossi V, Calne DB, Ruth TJ, Stoessl AJ. Dopamine release in human ventral striatum and expectation of reward. *Behav Brain Res*. 2002;136(2):359-363.
39. Buunk AM, Groen RJ, Veenstra WS, Spikman JM. Leisure and social participation in patients 4-10 years after aneurysmal subarachnoid haemorrhage. *Brain Inj*. 2015;29(13-14):1589-1596.

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