Fatigue after aneurysmal subarachnoid hemorrhage:

A study of risk factors, clinical presentation and treatment with (−)-OSU6162

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Elin Western

Summary

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is a debilitating disease leaving many patients with long lasting cognitive and emotional problems as well as a feeling of constant exhaustion, referred to as fatigue. Although identified as a leading cause of poor quality of life and inability to work after aSAH, fatigue is a challenging symptom to define, and, consequently, to measure and treat. The present thesis aims to increase the understanding of fatigue after aSAH (post-aSAH fatigue) with special emphasis on a potential treatment.

Objectives: The thesis aims to (1) assess the frequency and potential predictors for the development of post-aSAH fatigue (paper I), (2) explore features of post-aSAH fatigue and investigate its association with other commonly observed problems after aSAH (paper II), and (3) evaluate the efficacy of (−)-OSU6162, a stabilizer of the neurotransmitter dopamine, in the treatment of fatigue and other common sequelae after aSAH (paper III).

Patients and methods: In paper I, we conducted a telephone interview where the Fatigue Severity Scale (FSS), a patient reported outcome measure (PROM), was included to identify the presence and prevalence of fatigue in a large cohort of aSAH patients. Further, we also employed a univariable and multivariable logistic regression analysis with manual backward elimination comparing aSAH patients with and without fatigue (FSS mean score ≥4 and <4, respectively) to identify predictors from the acute phase for the development of fatigue in the chronic phase. Paper II and III were based on a double-blinded, randomized, placebo-controlled study of aSAH survivors with chronic fatigue. We performed an itemized analysis and correlation analyses on PROMs and cognitive test performances from baseline assessment (paper II). Further, primary and secondary outcome measures (PROMs and cognitive test performances) were used when evaluating the efficacy of (−)-OSU6162 as a treatment for fatigue and other commons symptoms after aSAH (paper III).

Results: Fatigue was present in 69.7% aSAH patients and it was relatively stable over time. Multivariable regression analysis showed that a history of nicotine use, reduced consciousness (Glasgow Coma Scale score <14) at admission and severe vasospasm during the acute phase were independent predictors that all more than doubled the risk to develop fatigue in the chronic phase after aSAH. Survivors of aSAH with chronic fatigue experienced their fatigue as being one of the most disabling symptoms and characterized it as predominated by low motivation, mental exhaustion and a heightened sensitivity to stress. Fatigue due to physical

exercise was the least bothersome aspect of fatigue, and weight gain was associated with depressive symptoms and not fatigue. Although a strong relationship was found between fatigue and emotional problems, especially depression, the overlap was incomplete. Further, fatigue was not associated with neurological outcome nor cognitive functioning, but related to poor health-related quality of life (HRQoL) and partially contributed to low ability to return to work (RTW). In a double-blind, randomized, placebo-controlled study, 96 patients with post-aSAH fatigue were randomized to treatment with (−)-OSU6162 (n=49) or placebo (n=47). Both groups showed significant improvement on the primary outcome measure, the Fatigue Severity Scale (FSS), after 12 weeks of treatment. However, significant differences between groups could not be demonstrated. Improvement in mental fatigue (the Mental Fatigue Scale), vitality (as measured with Short Form Health Survey, 36-item), and depressive symptoms (the Beck Depression Inventory-II) was also observed for both groups after 12 weeks of treatment, whereas improvement in anxiety symptoms (Beck Anxiety Inventory) was found in the placebo group only. Cognitive test performances were in general unaffected by treatment in both groups. In subgroup analyses, we found an effect of (−)-OSU6162 on fatigue (FSS) for patients who had resumed their previous workload in their occupation. Further, the efficacy of (−)-OSU6162 regarding fatigue (FSS) was improved with concomitant use of antidepressants at week 1 and 12 of treatment beyond the placebo response. Also, concomitant use of beta-or calcium channel blockers improved the efficacy of (−)-OSU6162 on mental fatigue (MFS) at week 4 of treatment beyond the placebo response. (−)-OSU6162 was found to be safe and well tolerated.

Conclusions: Post-aSAH fatigue was a frequent and long-lasting symptom characterized as a mental type of fatigue related to poor HRQoL and partially to inability to work. Post-aSAH fatigue was also strongly related to depression, but the overlap was incomplete and implied that the two constructs should be treated separately. Reduced consciousness at admission and severe vasospasm in the acute phase, as well as history of nicotine use, were independent predictors for the development of post-aSAH fatigue. Based on these findings in combination with recent evidence on the relationship between aSAH-related brain injury and neuroinflammation, we postulated pro-inflammatory cytokines causing dopamine imbalance as a common denominator for post-aSAH fatigue and the identified predictors. However, fatigue and other sequelae after aSAH were similarly alleviated by treatment with (−)-OSU6162 and placebo. A strong placebo response may be exploited in developing non-pharmacological rehabilitation programs for post-aSAH fatigue.

Sammendrag

Bakgrunn: En hjernehinneblødning som skyldes en sprukken utposning på hjernens arterier (aneurisme) kan medføre langvarige kognitive og emosjonelle problemer, samt en opplevelse av ekstrem utmattelse (fatigue). Selv om fatigue er en ledende årsak til redusert livskvalitet og svekket evne til å stå i arbeid, er det et symptom som har vist seg vanskelig å definere, og ikke minst måle og behandle. Denne avhandlingen har som mål å øke forståelse av fatigue etter hjernehinneblødning med spesiell vekt på en potensiell behandling.

Formål: Formålet med avhandlingen var å (1) kartlegge prevalensen og potensielle risikofaktorer for utviklingen av fatigue etter hjernehinneblødning (artikkel I), (2) utforske karakteristikker ved fatigue etter hjernehinneblødning og undersøke mulige assosiasjoner med andre typiske plager etter hjernehinneblødning (artikkel II), samt (3) evaluere effekten av (−)-OSU6162, en såkalt dopaminstabilisator, i behandlingen av fatigue og andre typiske plager etter hjernehinneblødning (artikkel III).

Pasienter og metode: I artikkel I gjennomførte vi telefonintervju i en stor kohort av aSAH pasienter hvor spørreskjemaet Fatigue Severity Scale (FSS) ble inkludert for å kartlegge prevalens av fatigue etter hjernehinneblødning. Videre sammenlignet vi hjernnehinneblødningspasienter med og uten fatigue (FSS gjennomsnittsskåre ≥4 eller <4, respektivt) for å identifisere risikofaktorer fra akutt fase for utviklingen av fatigue i senfase ved bruk av univariable og multivariable regresjonsanalyser. Vi gjennomførte også en dobbel-blindet, randomisert, placebo-kontrollert studie av hjernehinneblødningspasienter med fatigue. Vi analyserte responser og gjennomførte korrelasjonsanalyser basert på spørreskjemaer og kognitive testprestasjoner fra grunnlagsvurderingen (baseline) (artikkel II), samt evaluerte primær- og sekundæreffekt av (−)-OSU6162 som behandling av fatigue og andre plager etter hjernehinneblødning (artikkel III).

Resultater: Forekomsten av fatigue etter hjernehinneblødning var 69.7% og var relativt stabil over tid. Multivariabel regresjonsanalyse viste at nikotinbruk, redusert bevissthetsnivå (Glasgow Coma Scale score <14) ved innleggelse og alvorlig grad av vasospasmer nær doblet risikoen for utvikling av fatigue i senfase. Fatigue etter hjernehinneblødning kunne best karakteriseres som en svært hemmende og mental form for utmattelse preget av lav motivasjon og en dårligere toleranse for stress. Fatigue grunnet fysisk aktivitet var ikke fremtredende, og observert vektøkning var relatert til depressive symptomer og ikke fatigue.

Selv om det var en sterk sammenheng mellom depresjon og fatigue var det kun 1/3 av pasientene med fatigue som samtidig opplevde seg deprimert. Videre så vi ingen signifikant assosiasjon mellom fatigue og nevrologisk status, ei heller kognitiv fungering. Imidlertid var det er sterk sammenheng mellom fatigue og redusert helse-relatert livskvalitet og hvor fatigue var delvis bidragsytende til at pasienter ikke kom seg tilbake i arbeid. I vår dobbelt-blindet, randomiserte, placebo-kontrollerte studie ble 96 hjernehinneblødningspasienter med fatigue randomisert til behandling med (−)-OSU6162 (n=49) eller placebo (n=47). Begge gruppene opplevde mindre grad av fatigue (FSS) etter 12 ukers behandling, men det var ingen forskjell i grad av forbedring mellom gruppene. Videre var det også en bedring av mental fatigue (MFS), vitalitet (SF-36) og depressive symptomer (BDI-II) for begge grupper etter 12 ukers behandling, men bedring av angstplager (BAI) ble kun observert i placebogruppen. Kognitive testprestasjoner var generelt uaffisert av behandling for begge grupper. Subgruppeanalyser viste en positiv effekt av (−)-OSU6162 på graden av fatigue (FSS) for pasienter som var i fullt arbeid. Videre var det en positiv effekt av (−)-OSU6162 på graden av fatigue (FSS) i behandlingsuke 1 og 12 for pasienten som i tillegg brukte antidepressiva. Lignende var det en positiv effekt av (−)-OSU6162 på graden av mental fatigue (MFS) i behandlingsuke 4 for pasienter som i tillegg brukte betablokkere. (−)-OSU6162 ble godt tolerert og ga ingen alvorlige bivirkninger.

Konklusjoner: Fatigue etter hjernehinneblødning er et vanlig og vedvarende symptom karakterisert av en mental form for utmattelse relatert til redusert livskvalitet og delvis til manglende evne til å stå i arbeid. Fatigue etter hjernehinneblødning er samvariende med depressive plager, men fatigue og depresjon bør anses som to separate symptomer da overlappet mellom de to ikke er komplett. Redusert bevissthetsnivå ved innleggelse og alvorlig grad av vasospasmer i akutt fase, samt nikotinbruk før hjernehinneblødningen, er uavhengige risikofaktorer for utviklingen av fatigue i senfase. Basert på våre funn i kombinasjon med tidligere forskningslitteratur om inflammasjon i sentralnervesystemet etter hjernehinneblødning, postulerer vi at proinflammatoriske cytokiner og forstyrrelse av dopaminnivået i hjernen er fellesnevnere for fatigue etter hjernehinneblødning og risikofaktorene vi identifiserte. Imidlertid fant vi ingen overlegen effekt av (−)-OSU6162 sammenlignet med placebo i behandlingen av fatigue etter hjernehinnebløning. Placeboeffekten kan muligens utnyttes i utviklingen av ikke-farmakologiske rehabiliteringsintervensjoner for pasienter med fatigue etter hjernehinneblødning.

List of publications

The present thesis is based on the three papers listed below. They are referred to in the text by roman numerals.

I. Western, E., Sorteberg, A., Brunborg, C., & Nordenmark, T. H. (2020). Prevalence and predictors of fatigue after aneurysmal subarachnoid hemorrhage. *Acta neurochirurgica*, *162*(12), 3107–3116.

II. Western, E., Nordenmark, T. H., Sorteberg, W., Karic, T., & Sorteberg, A. (2021). Fatigue After Aneurysmal Subarachnoid Hemorrhage: Clinical Characteristics and Associated Factors in Patients With Good Outcome. *Frontiers in Behavioral Neuroscience*, *15*(94).

III. Western, E., Nordenmark, T. H., Sorteberg, W., Sorteberg, A., Karic, T., & Sorteberg, A. (2021). (−)-OSU6162 in the treatment of fatigue and other sequelae after aneurysmal subarachnoid hemorrhage: a double-blind, randomized, placebo-controlled study. *Journal of Neurosurgery (published online ahead of print)*, 1-11.

List of abbreviations

ACA; Anterior Cerebral Artery
ACoA; Anterior Communicating Artery
aSAH; Aneurysmal Subarachnoid Hemorrhage
BAI; Beck Anxiety Inventory
BDI-II; Beck Depression Inventory, 2nd edition
CBT; Cognitive Behavioral Therapy
CNS; Central Nervous System
CPP; Cerebral Perfusion Pressure
CPT-III; Connors' Performance test, 3rd edition
CSF; Cerebrospinal Fluid
CT; Computed Tomography
CTA; Computed Tomography Angiography
CVLT-II; California Verbal Learning Test, 2nd edition
DCI; Delayed Cerebral Ischemia
D-KEFS; Delis-Kaplan Executive Functions System
FSS; Fatigue Severity Scale
GCS; Glasgow Coma Scale
HH; Hunt and Hess Scale
HRQoL; Health-Related Quality of Life
IA; Intracranial aneurysm
ICA; Internal Carotid Artery
ICP; Intracranial Pressure
IL; Interleukin
INF; Interferon
LOCi; Loss of Consciousness at ictus
MCA; Middle Cerebral Artery
ME/CFS; Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MFS; Mental Fatigue Scale
MRA: Magnetic Resonance Angiography
MRI; Magnetic Resonance Imaging
MS; Multiple Sclerosis
PCA; Posterior Cerebral Artery
PCoA; Posterior Communicating Artery
PD; Parkinson's Disease
Post-aSAH fatigue: Fatigue after aneurysmal subarachnoid hemorrhage
PROMs; Patient-Reported Outcome Measures
PTSD; Post-Traumatic Stress Disorder
QTc; corrected QT interval
RTW; Return to Work
SF-36; Short Form Health Survey, 36-item
TBI; Traumatic Brain Injury
TNF-α; Tumor Necrosis Factor-alpha
WAIS-IV; Wechsler Adult Intelligence Scale, 4th edition
WFNS; World Federation of Neurosurgical Societies

1 Introduction

Subarachnoid hemorrhage, characterized by the accumulation of blood in the subarachnoid space, is a potentially life-threatening condition accounting for ≈5% of all strokes (1, 2). It can be the result of trauma, but the majority of cases (85%) are due to the rupture of an intracranial aneurysm (IA) (2, 3). The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is approximately 9-10 per 100 000 person-years (4, 5), but the mortality rate is as high as 45% (6, 7) in the western population. There is a clear female predominance (2:1) in adults (8) and it occurs most commonly between 40 and 60 years of age (9). Therefore, many of the aSAH survivors are in their most productive years with major responsibilities with respect to both work and family obligations.

Traditionally, research on aSAH has mainly focused on surgical and medical treatment in the acute phase with initial focus on survival. Consequently, improvement of survival rate (7) due to early intervention and advances in management has made the research on long term outcome increasingly relevant. Hence, a crucial question is quality of life after survival. Review studies (10-12) indicate that one third endure persistent cognitive and emotional problems known as the post-aSAH syndrome (13) even in the absence of neurological deficits. Among these problems, fatigue is the most prominent symptom and found in up to 90% of aSAH patients (12). Still, there is limited knowledge about fatigue after aSAH.

1.1 Aneurysmal subarachnoid hemorrhage

The occurrence of intracranial aneurysms (IAs) in the general population is low and ranges between 3% to 5% (14, 15). Most IAs will never rupture and the annual rupture rate is ≈1% (16, 17). IAs are characterized by localized structural deterioration of the arterial wall forming saccular pouches that develop at major branching cerebral arteries.

The brain receives blood from two pairs of arteries (see Figure 1): the internal carotid arteries (ICA) and the vertebral arteries. The ICAs enters the brain through a canal in the base of the skull and branch to form the middle cerebral arteries (MCA), which is the largest branch of ICA and supplies the major part of the cerebral cortex, and the anterior cerebral arteries (ACA). The ACAs, where each side are connected by the anterior communicating artery

(ACoA), projects forward over the optic nerve and runs along the medial side of the cerebral hemispheres. The vertebral arteries converge near the base of the pons to form the unpaired basilar artery. At the level of the midbrain, the basilar artery splits into the two pairs of superior cerebellar arteries and posterior cerebral arteries (PCA), where the latter sends branches called posterior communicating arteries (PCoA) that connects them to the ICAs. Thus, the arteries form a ring at the base of the brain called *the circle of Willis*. The majority of IAs are located in the anterior circulation (18).

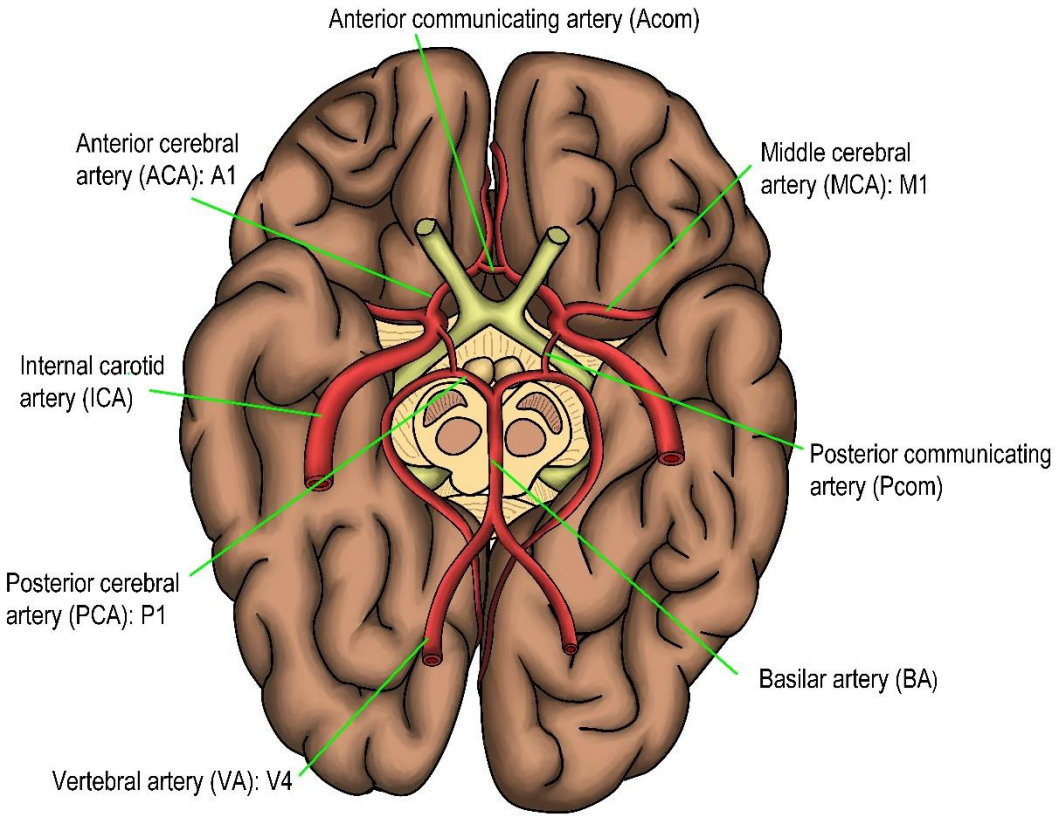

Figure 1. Schematic drawing of the arrangement of arterial vessels on the base of the brain. The diagram shows common locations of intracranial aneurysms within *the circle of Willis*. Adobe Stock.

Intracranial aneurysms are not congenital, but develop in the course of life. The exact reasons why IAs develop are unknown, but environmental exposition and genetic predisposition are of importance (19, 20). Smoking, hypertension and excessive alcohol intake are well-established modifiable risk factors for aneurysm formation and SAH (17, 21, 22) and may have an additive effect on IA formation (23). The uniqueness of smoking as a risk factor is that cumulative evidence have implied a causal relationship between cigarette smoking and the development of aneurysms and their subsequent rupture that is independent of other known

risk factors (24). Further, smoking has been linked to vasospasm, a common complication during the management of aSAH (24, 25). Nonmodifiable risk factors for aneurysm formation and SAH include increasing age, being female, positive family history, and autosomal-dominant polycystic kidney disease (4, 26-29).

The most dreaded complication of an IA is rupture (see Figure 2) and implies that blood pulses under arterial pressure into the subarachnoid space (subarachnoid hemorrhage) and often in addition into the ventricles (intraventricular hemorrhage) or the brain itself (intracerebral hemorrhage). When the aneurysm ruptures, the intra-arterial pressure (blood pressure) is transmitted through the brain within the fraction of a second and causes a vast increase in intracranial pressure (ICP) (30). The ICP increase may exceed mean arterial blood pressure, thus compromising or abolishing cerebral perfusion pressure (CPP) and leading to cerebral circulatory arrest. This circulatory arrest may be lethal for the patient, but it limits the extent of the hemorrhage. The ICP increase may spontaneously diminish, but if the increase in ICP is sustained over time, the ultimate consequence can be low or no blood flow to the brain and subsequently death.

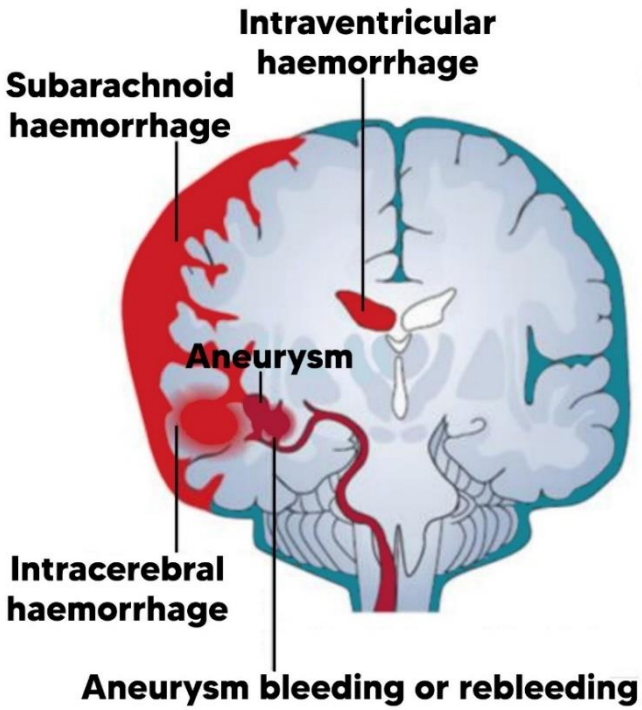

Figure 2. Illustration of aneurysm rupture and accumulation of blood in the subarachnoid space in combination with intracerebral hemorrhage and intraventricular hemorrhage. Adapted and modified from de Oliveira Manoel et al. (31), https://creativecommons.org/licenses/by/4.0

1.1.1 Clinical manifestations and diagnosis of aSAH

The classical symptom of an aneurysm rupture is sudden-onset and severe headache (often described as thunderclap headache or "the worst headache of my life", perfectly coined in the German language as "Vernichtungskopfschmerzen"), nausea and/or vomiting (3). Patients most often present with light sensitivity and nuchal rigidity. Early-onset seizures are not uncommon (32, 33) and up to 40% experience an initial loss of consciousness at the time of ictus (LoCi) presumed to result from transient intracranial circulatory arrest (34). However, the above symptoms are nonspecific. Therefore, neurodiagnostics and imaging is necessary to decide whether the clinical manifestations are compatible with aSAH.

When a patient with suspected SAH is admitted to the hospital, neuroimaging is important for diagnosis and management (35, 36). Computerized tomography (CT) scans are highly sensitive (approaches 100%) for the detection of SAH within the first 6 hours (35) and is the first test of choice also due to its availability. The CT scan can identify the amount and extent of subarachnoid blood (modified Fisher grade) (37) and intraventricular blood (modified LeRoux score) (38). In cases of high clinical suspicion of SAH, a negative CT scan is often followed by a lumbar puncture for detecting xanthochromia (bilirubin) in the cerebrospinal fluid (CSF). However, it is recommended to substitute lumbar puncture with non-contrast magnetic resonance imaging (MRI) (39) to further investigate false negative initial CT results for SAH. Although fluid-attenuated inversion recovery, susceptibility-weighted imaging and diffusion-weighted imaging sequences are particularly useful, MRI is less optimal in the acute diagnosis of SAH due to longer acquisition time and difficulty of use in critically ill patients'.

When SAH is discovered, the diagnostics proceeds to vascular imaging to determine the underlying cause. Digital subtraction angiography or foremost CT angiography (CTA) are common used tools to visualize the localization and anatomical configuration (neck/dome ratio) of an IA, but also MR angiography (MRA) can be effective (36). Vascular imaging is important in determining etiology for non-traumatic SAH. When an IA is confirmed, it can further utilize optimum selection of aneurysm repair method.

Hence, even though the incidence of IA formation and rupture is low in the general population, a subarachnoid hemorrhage due to rupture of an IA is a dramatic event with a potential deadly outcome. If a patient survives the initial bleed, the premises for recovery and

independence are at large determined by the cascade of complex pathophysiological events during the acute phase.

1.1.2 Management of aSAH and complications during admission

Hemorrhage into the subarachnoid space initiates a complex cascade of deleterious events that can cause damage to the central nervous system (CNS). Therefore, early management of aSAH is essential to prevent or minimize the development of brain injury which is the primary cause of mortality (40).

The neurological condition of a patient, which is an indication of cerebral damage or dysfunction, can change during the clinical course. Therefore, a reliable and valid grading system for the assessment of aSAH patients is necessary. A widely used scale is Hunt and Hess (HH) (41). The scale ranges from 1 to 5, with 5 indicating the worst clinical condition. Besides the level of consciousness (drowsiness, stupor or deep coma), headache (minimal, moderate or severe), neck stiffness (slight nuchal rigidity versus nuchal rigidity) and focal neurological deficits (mild, moderate or severe hemiparesis) constitutes this scale. The Glasgow Coma Scale (GCS) (42) is another commonly used scale to assess the depth and duration of impaired consciousness. It measures motor responsiveness, verbal performance and eye opening on a scale from 3 to 15, with 15 indicating no alternation in performance. Based on the GCS, the World Federation of Neurosurgical Societies (WFNS) (43) proposed a grading scale of five levels including the presence or absence of focal neurological deficits, to grade the clinical severity of aSAH. Historically, physicians have been reluctant to treat aSAH patients presenting in a poor clinical state (deeply comatose, HH and WFNS 5), but studies of cognitive function and quality of life justifies the current paradigm shift towards early and aggressive care of all aSAH cases (44-46).

The patient's condition at admission, particularly the level on consciousness, is one of the most important determinant for outcome after aSAH (47). Loss of consciousness at ictus (LOCi) is the result of a dramatic increase in ICP and reduction in CPP. In combination with the direct mass effect of blood on midbrain and cortical structures, this leads to transient reduction in cerebral blood flow, hence prolonged LOCi is strongly associated with poor clinical grade at admission (34). Ultimately, the results of LOCi can be ischemic injury and

potentially lead to cerebral infarction, which in turn initiates a cascade of pathophysiological events (48). Studies have demonstrated that LOCi is an important manifestation of early brain injury and a predictor of unfavorable functional outcome after aSAH (34, 49, 50).

About 8-23% of patients who recover from the initial hemorrhage experience rebleeding during the first 72 hours, where the majority (up to 90%) of rebleeding episodes occurs within the first 6 hours of the primary bleed (51, 52). Even though rebleeding is a complex and multifactorial event where the exact mechanisms are unestablished, it has been found to be a leading cause of morbidity and mortality after aSAH (6, 53). Therefore, the risk of rebleeding highlight the need for early aneurysm repair in combination with antifibrinolytic drug treatment (systemic administration of tranexamic acid) (51).

Aneurysm repair aims at excluding the aneurysm from the circulation. The best method of aneurysm repair chosen for each patient depends on both individual factors (age, clinical condition at admission) and aneurysm characteristics (location, size and morphology) (54). Two major treatment options are available: Microsurgical aneurysm repair (55, 56), also referred to as clipping, involves craniotomy and placement of a clip across the aneurysm neck to cut it off from the cerebral circulation. In endovascular aneurysm repair (57), also referred to as coiling, exclusion from the cerebral circulation is achieved by occlusion and stagnation of flow within the aneurysm. The aneurysm is packed with metal treads (coils) through a microcatheter. Figure 3 illustrates surgical and endovascular treatment for aneurysm repair, respectively. The presence of multiple aneurysms and need for additional devices, such as stents or flow diverters, will also influence the choice of aneurysm repair method.

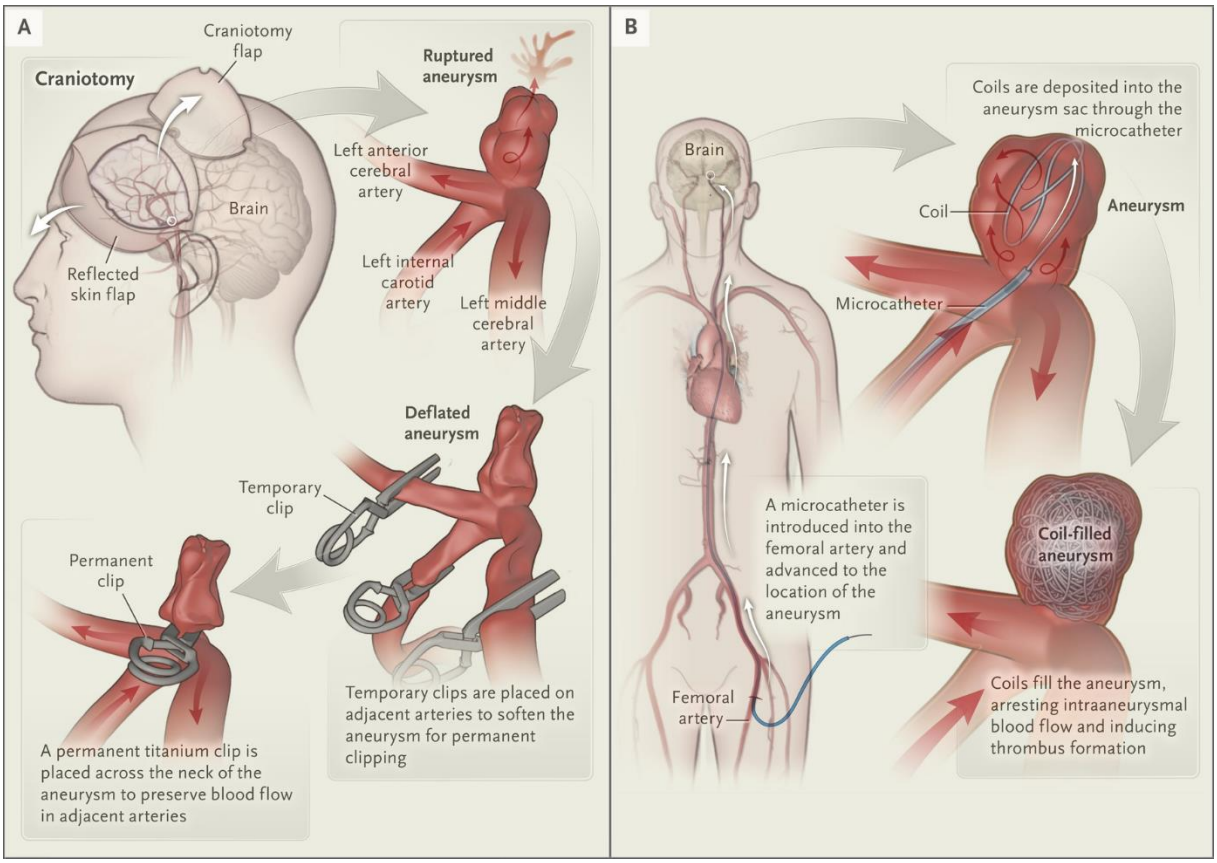

Figure 3. Microsurgical aneurysm repair (**A**) involves exposing the aneurysm and the adjacent normal arteries by craniotomy so that the neurosurgeon can apply a titanium clip of the neck of the aneurysm. Endovascular repair (**B**) involves the navigation of a microcatheter through the circulation until the catheter tip is in the lumen of the aneurysm where platinum coils are delivered and packed. Adapted and modified with permission from Lawton and Vates (58), Copyright Massachusetts Medical Society.

Hydrocephalus, characterized by an abnormal buildup of CSF in the ventricles, is a well-recognized complication after aSAH and can occur in all stages (acute, subacute and chronic phase) after the initial ictus. Acute hydrocephalus may be caused by obstruction of CFS flow in the tentorial hiatus due to extensive hemorrhage in the perimesencephalic cistern or in the ventricles, or due to extensive fibrosis in the subarachnoid space and inflammatory responses (47, 59). Hydrocephalus is typically diagnosed based on the size of the ventricles on CT imaging. Acute hydrocephalus with a need for external ventricular drainage or lumbar drainage develops in 15% to 87%, where approximately 8.9% to 48% require insertion of a permanent CFS diversion (a ventriculoperitoneal shunt) due to development of chronic hydrocephalus (39). Predictors for shunt-dependent chronic hydrocephalus following aSAH are a combination of severity of hemorrhage (such as extent of intraventricular hemorrhage)

and complications during the acute and subacute phase (60, 61). Both acute and chronic hydrocephalus has been related to poor neurological outcomes and cognitive deficits (59, 62).

When worsening occurs during the clinical course, it can also be the result of cerebral ischemia which occurs in ≈30% of patients surviving the initial hemorrhage (63). Because cerebral ischemia typically occurs between day 3 and 10 after the hemorrhage, the complication is often called delayed cerebral ischemia (DCI) (64). Clinical worsening attributable to DCI is a diagnosis *per exclusionem*, that is when other possible causes of deterioration (such as infection, hydrocephalus, hyponatremia and others) have been eliminated (65). Typical clinical features of cerebral ischemia is focal neurological signs or a decrease in the level of consciousness of more than 2 GCS points and exceeding the GCS fluctuation that have been observed in the particular patient. The presence of DCI during the hospital course has shown to be a strong predictor of cognitive deficits (66). However, the exact pathogenesis of cerebral ischemia after aSAH is unknown and constitutes multiple causes (such as neuroinflammation, microthromboembolism, impaired cerebral autoregulation and cortical spreading depolarization) (67, 68), but angiographic vasospasm is the best-documented component of DCI.

Cerebral vasospasm is the segmental or diffuse narrowing of cerebral arteries (69). The peak incidence of cerebral vasospasm is seen day 7 to 8 post-ictus, but several studies also demonstrate ultra-early angiographic vasospasm occurring within 48 hours of aneurysmal rupture (70, 71). Symptomatic vasospasm occurs in 20% to 40% of aSAH patients and typically refers to clinical worsening deemed secondary to vasospasm after other possible causes of deterioration have been eliminated while angiographic vasospasm, as confirmed by Digital Subtraction Angiography, CTA, MRA, or Transcranial Doppler Ultrasonography, occurs in up to 70% of patients (72). As can be seen, the relationship between symptomatic vasospasm and angiographic vasospasm can be inconsistent. To complicate matters further, the concept of DCI is often used interchangeably with symptomatic vasospasm, infarction detected on CT scan attributable to vasospasm, or both. While vasospasm or arterial narrowing is associated with DCI, the former has been distinguished from clinical neurological worsening related to ischemia and infarction based on radiographic evidence referred jointly as DCI (72, 73).

Signs of DCI may progress to cerebral infarction in 11% to 20% of aSAH patients (74-76), where the latter represents irreversible lesions detected on neuroimaging. It has been

suggested that severe SAH evident on CT scan (25) and neuroinflammation (77-79) are strong risk factors for the development of cerebral vasospasm, which in turn can result in cerebral hypoperfusion and trigger cell death processes (80), and further lead to infarction which is associated with poor outcome (81-83). Even though there are an undisputed association between angiographic vasospasm and DCI (76, 84), more than half of patients with moderate to severe vasospasm do not develop infarction (85). In addition, up to 25% of infarcts on CT are not in the same area as the vessel narrowing (75, 86) where the pattern of infarction often is diffuse and cortical (86). Also, a review conducted by Etminan and colleagues (87) showed that a significant reduction of angiographic vasospasm did not correlate with better functional outcomes. In contrast, improved outcomes corresponded to lower incidence of cerebral infarction.

As mentioned above, hemorrhage into the subarachnoid space initiates a complex cascade of deleterious events that can cause brain injury. Inflammation is a natural response to infection and tissue damage. However, the inflammatory response in cerebral tissue following cerebral ischemia can contribute to the progression of brain injury and exacerbation of neurological deficits. The inflammatory response is characterized by the production and release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-12, IL-18, IL-20 and interferon-gamma (INF-γ). The aforementioned cytokines are suggested in the involvement of brain injury related to cerebral ischemia (88).

Recent research has highlighted the need for knowledge about these damage-associated molecular patterns that results from the breakdown of blood in the subarachnoid space, which ultimately triggers the release of pro-inflammatory cytokines leading to DCI and potential brain injury (85, 89, 90). In a review by Lucke-Wold et al. (91), it was stated that the release of pro-inflammatory cytokines can be linked to the development of cerebral vasospasm and DCI. In a scoping systematic review by Zeiler et al. (92), the strongest association with poor outcome after aSAH were found for elevated CSF levels of the following cytokines: IL-6, IL-1ra, IL-8, and TNF-α/soluble tumor necrosis factor receptor. This was further supported by de Oliveira Manoel and Macdonald (93), which stated that a systemic immune response activation after SAH is commonly manifested by high levels of cytokines such as IL-1, IL-6 and TNF- α – all described as key mediators of systemic inflammation. Emerging data also suggests that cytokines target subcortical structures in the brain including basal ganglia and dopamine function (94, 95). It has been generally accepted that dopamine acts as a key

neurotransmitter in the brain and numerous studies have shown that it can be viewed as a "brain conductor" regarding the organization of behavior (96, 97).

1.1.3 Common sequelae after aSAH

In a comprehensive review of the cognitive and functional impairment after aSAH (98), it was shown that deficits in the domains of memory (up to 60%), executive function (up to 75%) and language (up to 75%) were common sequelae of aSAH. Further, impairments were also shown for functional outcome measures such as daily functioning, health-related quality of life (HRQoL) and return to work (RTW). In an updated systematic review (10), cognitive impairment was prevalent (40-70%) even for patients who were initially discharged with good neurological outcome. Therefore, it was stressed that gross neurological outcome measures, such as modified Rankin Scale and Glasgow Outcome Scale, are not reliable predictors of long-term cognitive deficits. These cognitive deficits, albeit relatively small compared to preictal cognitive status in many of the patients, can cause difficulties in daily functioning and when trying to resume work.

As can be seen by the two review studies mentioned above, subtle cognitive impairment and real-world deficits after aSAH can go undetected and lead to struggles with an invisible dysfunction when trying to resume pre-ictus obligations. Extensive research has also shown that emotional symptoms (such as depression, anxiety and PTSD) are common after aSAH (10, 98-102). In a recent systematic review by Tang et al. (11), depression was frequent (weighted proportion of 28.1%) and seemed to persist several years after the initial hemorrhage. Approximately one third of aSAH patients develop a post-aSAH syndrome consistent of cognitive and emotional problems, where fatigue is the most prominent symptom (13).

1.2 Fatigue

The word ‘fatigue’ is widely used in the clinical setting and research literature, but there is no consensus regarding a definition to fully account the experience of the ‘fatigued’ patient. Clinical descriptions often draw upon the original meaning of the word *fatigue* which has French (1660s) and Latin roots (15c.): “that which causes weariness” and “to weary, to tire out”, respectively (103). Healthy individuals also experience fatigue and it is a common complaint in the general population (104, 105) and frequently reported in primary care (106-108). Fatigue can be viewed as a normal and adaptive function in response to prevention of injury or dealing with infection (109), but pathological when the adaptive function has been lost. Further, it is a presumption that a “normal” experience of weariness, as opposed to pathological fatigue, is predictable, transient, responsive to rest, and does not interfere significantly with daily activities (110). However, the distinction between normal and pathological fatigue in not clear-cut.

In the only systematic review of fatigue after aSAH (12), prevalence of fatigue ranged between 31% and 90% considerably exceeding the prevalence of fatigue in the general population in Nordic and Western countries (18.3-23.1%) (105, 111, 112). Fatigue was most frequently reported during the first year after the hemorrhage (<1 year 73.6%), but was also highly prevalent in the chronic phase (≥1 year 50.7%) (12). In addition, a recent study (113) has demonstrated the presence of moderate to severe mental fatigue in up to 38% aSAH survivors more than 15 years after the hemorrhage. Even though the documentation is somewhat limited, it seems that fatigue is a frequent and long-lasting symptom after aSAH. The large variations in estimates of post-aSAH fatigue may be partly due to a number of methodological differences between studies. Nevertheless, even in studies that employ the same scale and cut-off score, the variation of estimate is still considerable.

Since aSAH is a type of stroke (acquired brain injury due to a vascular event), the evidence regarding post-stroke fatigue may be comparable to that of post-aSAH fatigue. In two systematic reviews and meta-analysis published the last five years, Cumming et al. (114) found the pooled prevalence estimate to be 50% (95% CI 43-57%) and Alghamdi et al. (115) found an estimate of 48% (95% CI 42-53%). That is, at some point after stroke approximately half of the patients suffered from fatigue. Especially the result regarding higher prevalence of fatigue after hemorrhagic stroke than those that suffered from ischemic stroke (66% versus

36%, $p < 0.001$) (115) might suggest that fatigue estimates may be even higher for aSAH than for stroke in general. Further, fatigue after stroke has been ranked as one of the top research priorities (116).

Meta-analysis' of fatigue exclusively after aSAH are nonexistent. Therefore, a presentation of all known studies reporting prevalence of post-aSAH fatigue are listed in Table 1.

Table 1. Summary of studies reporting frequency of fatigue after aSAH

Single question to diagnose fatigue

Study	**Design**	**N=**	**Age mean (range) ±SD**	**Sex, female**	**Aetiology of SAH**	**Timing after SAH**	**Tool**	**% with fatigue**
Eskesen et al. 1984 (117)	Longitudinal	42	50 (27-66)	45.5 %	Unknown	36 (3-64) m	SQ Y/N	41% (CI 95% 26-58%)
Ogden et al. 1997 (118)	Cross-sectional	123	48.8 ± 14.2	66.0 %	Not specified	4 - 7 y	SQ Y/N	35%
Hellawell et al. 1999 (119)	Longitudinal	44	49.7 ± 14.6	54.5 %	Aneurysmal, 80 %	6 m, 1 y, 2 y	SQ (HISC)	64%, 59%, 68%
Powell et al. 2004 (120)	Longitudinal	48	46.0 ± 10.0	67.0 %	Aneurysmal	9, 18 m	SQ 3 point scale	Moderate: 62%, 65%; Severe: 19%, 10%
Schuiling et al. 2005 (121)	Longitudinal	83	53.3 ± 12.1	70.0 %	Aneurysmal, 82 %	1 - 3.4 y	SQ Y/N (SDL)	31% (CI 95% 21-42%)
Passier et al. 2010 (122)	Cross-sectional	111	52.8 ± 13.0	82.0 %	Aneurysmal	3 m	SQ Y/N (CLCE-24)	90.1%

Specific questionnaire or diagnostic tool to diagnose fatigue

Study	**Design**	**N=**	**Age mean (range) ±SD**	**Sex, female**	**Aetiology of SAH**	**Timing after SAH**	**Tool**	**% with fatigue**
Rödholm et al. 2001 (123)	Longitudinal	63	51.2 ± 12.1	75.0 %	Aneurysmal	12 m	AED in the LM/OPD	Mild AED: 21% Moderate AED: 18%
Rödholm et al. 2002 (124)	Longitudinal	63	51.2 ± 12.1	75.0 %	Aneurysmal	3, 6, 12 m	AED in the LM/OPD	60%, 49%, 38%
Noble et al. 2008 (125)	Longitudinal	105	52.4 ± 11.0	57.0 %	Aneurysmal, 73.3 %	3, 13 m	MFSI-SF	59%, 36%
Visser-Meily et al. 2009 (126)	Cross-sectional	141	51.4 ± 12.3	67.0 %	Aneurysmal	2 - 4 y	FSS	67%

Passier et al. 2011 (127)	Cross-sectional	141	51.4 ± 12.3	67.0 %	Aneurysmal	2 – 4 y	FSS	67%
Passier et al. 2011 (128)	Longitudinal	108	53.4 ± 12.3	82.4 %	Aneurysmal	1 y	FSS	71%
Vetkas et al. 2013 (129)	Cross-sectional	114	54.0 ± 13.0	68 %	Aneurysmal	1 – 10 y	EST-Q	47%
Buunk et al. 2015 (130)	Cross-sectional	200	58.7	63.5 %	Aneurysmal	2 – 10 y	BISC	66%
Booerboom et al. 2016 (131)	Longitudinal	76	53.8 ± 11.5	68.4 %	Aneurysmal	0.4 – 3.9 y	FSS	60%
Khajeh et al. 2016 (132)	Longitudinal	84	55.7 ± 11.9	67 %	Aneurysmal	6 m, 14 m	FSS	50%, 60%
Buunk et al. 2018 (133)	Cross-sectional	221	54.0 ± 10.0	68.7 %	Aneurysmal, 75.1%	3 - 10 y	DMFS	Mental fatigue: 48.4 % Physical fatigue: 38.5%
Sörbo et al. 2019 (134)	Cross-sectional	44	57 (36-76)	75.0 %	Aneurysmal	1 y	MFS	57 %
Samuelsson et al. 2021 (113)	Cross-sectional	46	70	58.7%	Aneurysmal	15 - 21 y	MFS	25% (endovascular) 38.8% (microsurgical)
De Vries et al. 2021 (135)	Cross-sectional	59	53.0 ± 10.8	64.4%	Aneurysmal	4 y	FSS	59.3%

Abbreviations: Singel Question = SQ; Yes/No Answer = Y/N; HISC = Head Injury Symptom Scale; SDL = Sleep Diagnosis Questionnaire; CLCE-24 = Checklist for Cognitive and Emotional Consequences following stroke; The Lindqvist & Malmgren (LM) diagnostic system for organic psychiatric disorders (OPD) = LM/OPD; Astheno-emotional disorder = AED; Multidimensional Fatigue Symptom Inventory-Short Form = MFSI-SF; Fatigue Severity Scale = FSS; Emotional State Questionnaire = EST-Q; Brain Injury Symptom Checklist = BISC; Dutch Multifactor Fatigue Scale = DMFS; Mental Fatigue Scale = MFS.

1.2.1 Definition and operationalization of fatigue

In the absence of specific diagnostic criteria (with the exception of myalgic encephalomyelitis/chronic fatigue syndrome) to differentiate pathological fatigue from normal exhaustion, a framework of fatigue in neurological disorders has been proposed by Chaudhuri and Behan (136) where fatigue is defined as "*difficulty in initiation of or sustaining voluntary activities"* (p. 978). The authors differentiate between peripheral fatigue at the muscular level (physical fatigue) and fatigue related to the subjective sense of mental exhaustion perceived at the level of the central nervous system (central fatigue), where the latter has a cognitive component (mental fatigue). Central fatigue can lead to limitation in abilities to sustain concentration and endure mental tasks. A common denominator for both peripheral and central fatigue seems to be motivation, where expected rewards and benefits modulate the effort in any given situation. Consequently, central fatigue may depend on deficits in the balance between motivational inputs and/or energy expenditure (137, 138).

Further, a definition of fatigue been proposed by Staub and Bogousslavsky (139) for the stroke population. They define post-stroke fatigue as being "*a reversible decrease or loss of abilities associated with a heightened sensation of physical or mental strain, even without conspicuous effort, an overwhelming feeling of exhaustion, which leads to inability or difficulty to sustain even routine activities and which is commonly expressed verbally as a loss of drive"* (p. 76). Further, a case definition for post-stroke fatigue has also been formulated by Lynch et al. (140). For community patients the definition is as follows: "*Over the past month, there has been at least a 2-week period when patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities"* (p. 543).

The definitions for post-stroke fatigue as proposed above are descriptions of a subjective state of a certain duration with negative behavioral consequences, but remains unspecific to the underlying diagnosis. These definitions also points to the more commonly accepted fact that fatigue is a complex and multidimensional construct related to mental, emotional and physical experiences. One of the many challenges of defining fatigue, as stated by Kluger and colleagues (141), is to identify the distinct domains of fatigue and to distinguish it from related phenomena. They have proposed a unified taxonomy for fatigue in patients with

neurological illnesses, where they discriminate between perceptions of fatigue (i.e., subjective) and performance fatigability (i.e., objective).

No specific definition or extensive descriptions of post-aSAH fatigue have been made to date, even though two qualitative studies (142, 143) have highlighted the patient's perspective upon fatigue and other common symptoms after aSAH. However, Johansson and Rönnbäck (144) have given a clinical description of a mental type of fatigue after traumatic brain injury (TBI) which is strikingly similar to the statements made by aSAH survivors when trying to explain one of their main struggles. Johansson and Rönnbäck describes mental fatigue as a dynamic process with variation in mental energy levels that are severely affected by even tiny loads of sensory stimulation and/or with an inability to perform cognitive tasks over an extended period. Further, another typical feature of mental fatigue is a disproportionally long time needed to recover.

Therefore, in the absence of concrete diagnostic criteria to differentiate post-aSAH fatigue from normal exhaustion or tiredness, the definition of fatigue in this thesis is based on Kluger and colleagues (141) taxonomy stressing the subjective experience of fatigue in combination with Chaudhuri and Behan's (136) concept of central fatigue: *a subjective perception of mental exhaustion and enhanced perception of effort with a difficulty in initiation of or sustaining voluntary activities.*

1.2.2 Mechanisms behind fatigue

Although there are several studies that have investigated the pathogenesis of brain injury secondary to aSAH (see section 1.1.2), there is a knowledge gap on how these factors can be understood in relation to post-aSAH fatigue. Nevertheless, a handful of studies have studied the association between fatigue and mainly functional outcome measures, and to a certain degree predictors, which can give clues to potential mechanisms and underlying pathophysiology of post-aSAH fatigue. Further, culminating empirical evidence regarding possible mechanisms of fatigue in other disorders are presented below.

1.2.2.1 Associations with and predictors of post-aSAH fatigue

Already in 1999, Hütter and colleagues (145) presented evidence of mechanisms for aSAH-related brain injury in relation to functional outcome measures. Again, it was stressed that gross neurological outcome measures (such as Glasgow Outcome Scale) are adequate in the global predictions about the efficacy of neurosurgical treatment, but its suitability was doubted in assessment of psychosocial functioning after aSAH. Further, it was questioned if a so-called good outcome justified the assumption of no relevant neurobehavioral abnormalities. However, no studies in the review by Hütter et al. conducted analyses enabling a direct statistical comparison of fatigue and other outcome measures. It is only in the last two decades that the joint study of fatigue and aSAH have been a distinct focus.

Rödholm et al. (124) studied the presence of organic psychiatric disorders after aSAH. They found a higher frequency of pre-existing arterial hypertension among aSAH patients diagnosed with asteno-emotional disorder, characterized by cognitive deficits, fatigability, irritability, emotional instability and impaired stress tolerance, than the other organic psychiatric disorders. No significant association was found between age, reaction level (median RLS85 level), median WFNS grade, and amount of subarachnoid blood (median Fisher grade) and the asteno-emotional disorder patients when compared to the patients without organic psychiatric disorders. Neither were any differences between medians of acute hydrocephalus grades found between any of the organic psychiatric disorders groups. The possible association between post-aSAH fatigue and long-term pituitary dysfunction has been investigated. Khajeh et al. (132) included 84 aSAH survivors with long-term pituitary dysfunction, in particular patients with growth hormone deficiency. The authors found that severity of SAH (measured with WFNS score higher than 1) was associated with fatigue, but there were no effect of pituitary dysfunction or growth hormone deficiency on fatigue. Buunk et al. (133) assessed both patients with aSAH and angiographic negative SAH between 3 and 10 years after SAH. In a two-way ANOVA with both SAH types and external CSF drainage as independent variables and mental fatigue as dependent variables, only a significant main effect of external CSF drainage on mental fatigue was found. This was not the case for physical fatigue. In a study by Passier et al. (128), cognitive impairment at 3 months was significantly associated with fatigue 1 year after ictus.

Since all residual deficits can negatively affect daily functioning and well-being, the majority of studies investigating post-aSAH fatigue have explored its relationship with psychosocial and real-world functioning. It is generally well documented that reduced HRQoL is a common sequel after aSAH (98, 102, 146, 147). Visser-Meily et al. (126) found that post-aSAH fatigue was associated with reduced Quality of Life in a multivariate regression analyses. Further, Quality of Life scores showed a diverging pattern of good physical functioning after aSAH, but problems in the emotional and social domains. Vetkas et al. (99) found that post-aSAH fatigue was the most frequent symptom and independently related to all subscales of HRQoL measured. In the latter study, no relationship was found between fatigue and the time-interval from ictus. Problems in leisure activities and resumption of social activities has also been shown to be associated with post-aSAH fatigue, along with depressive symptoms and cognitive problems, in a study by Buunk et al. (130). Powell et al. (120) found that fatigue was associated with lower social participation (lower independence in Self-organization and lower levels of Socializing). The cause-effect relationship in the presented studies are debatable, where fatigue can be as much a consequence as a cause of failure to resume an active lifestyle with good quality of life.

Since a sudden rupture of an intracranial aneurysm is an unpredictable, life-threatening and potential traumatic event, many patients may develop emotional problems of clinical significance (11, 98, 102, 148). Passier et al. (128) found in aSAH patients without physical or cognitive impairments that fatigue in the chronic phase was associated with the presence of depression, anxiety, and passive coping style assessed 3 months after ictus. The authors discussed the uncertainty of whether maladaptive coping style and emotional problems are a result of the SAH itself, or if these factors are related to premorbid personality factors such as neuroticism. In a study by Noble et al. (101), 37.1% met the diagnostic criteria for post-traumatic stress disorder (PTSD) at both 3 and 13 months post-ictus. The patients with PTSD reported significantly more fatigue than those without PTSD. Sleep problems were also associated with PTSD. The authors therefore suggested that PTSD induced sleep problems, which in turn lead to fatigue. Buunk et al. (133) found moderate correlations between mental fatigue and symptoms of anxiety and depression (on the Hospital Anxiety and Depression scale).

Even though a majority of aSAH survivors does not have significant neurological and physical deficits, a surprisingly low rate of patients are capable of returning to work (13, 127). Buunk et al. (149) conducted one of the few known studies exploring the relationship between

post-aSAH fatigue and RTW. They found that mental fatigue was significantly associated with low rate of RTW. Physical fatigue was also related to RTW (*d* 0.94), but effect size was higher for mental fatigue (*d* 1.13). Moreover, mental fatigue was the best predictor of functional outcome in the chronic stage as compared to physical fatigue and mood disorders.

1.2.2.2 Risk factors and postulated mechanisms for fatigue in other disorders

For the "stroke family of events", it was stated in a review by De Doncker and colleagues (150) that preliminary evidence supported the idea of early biochemical imbalance resulting in altered homeostasis as a result of the stroke. The authors stressed the need for more research on the inflammatory factors that appears to play a role in the early development of post-stroke fatigue, but underlined that it is yet unclear if there are biochemical imbalances that might account for post-stroke fatigue in the chronic phase. They further concluded that lesion location did not seem to be a determinant of post-stroke fatigue, also stated by Chaudhuri and Behan (136) for neurological disorders in general. Hence, there is a growing evidence of a relationship between cytokines and cerebrovascular diseases (151-153).

Fatigue is not specific or exclusive for aSAH or stroke in general, but a prominent symptom in many other illnesses (136, 154). Multiple sclerosis (MS), also known as encephalomyelitis disseminate, is a demyelinating disease where the insulating covers of nerve cells in the CNS are damaged. Fatigue is the most commonly reported complaint in those with MS and four potential pathophysiological mechanisms of MS-related fatigue have been highlighted in a review by Manjaly et al. (155): white and grey matter lesions in the brain, immunological and inflammatory processes, maladaptive network recruitment in the brain due to lesions or inflammation, and metacognition on fatigue. There is growing evidence of immunological factors, such as pro-inflammatory cytokines, and their contribution to MS-related fatigue (156) with converging evidence from neurophysiology and imaging studies that suggests fatigue in MS may be related to dysfunction of cortico-subcortical circuits (thalamus, basal ganglia and frontal cortex) (157-159).

Parkinson's disease (PD) is a long-term degenerative disorder of the CNS that mainly affects the motor symptom. However, fatigue is one of the most common non-motor symptoms of PD (160) and prevalence estimates are similar to that of stroke (161). Fatigue in PD has been

linked to structural changes in caudate and putamen, particularly in the dorsal striatum (162). Others have suggested that non-motor symptoms in PD patients, such as fatigue and depressive symptoms, might be the result of inflammatory mechanisms and pro-inflammatory substances (163). In a recently published review (164), Wang et al. stressed that neuroinflammation is a pathological hallmark of PD. They referred to several studies implicating that especially pro-inflammatory cytokine IL-6 could detect fatigue and become a valid predictor of fatigued PD patients.

Symptoms following traumatic brain injury (TBI) includes a wide range of physical, cognitive and emotional problems, where fatigue is prominent. The underlying mechanisms of fatigue after TBI are unclear, where a systematic review by Mollayeva et al. (165) points to a range of factors associated with fatigue - from premorbid status, injury-related factors, comorbid symptoms and to the patients' perception of fatigue. The authors state that future research should focus on the variety of lesions from TBI, inter-individual variability in perception of fatigue and multifactorial fatigue etiology. Since low-grade neuroinflammation follows TBI, Johansson and Rönnbäck (144) consider metabolic failure as one probable explanation for fatigue after TBI. In a review by Tapp et al. (166), it was suggested that hypothalamic-pituitary-adrenal axis dysfunction is prevalent and contributes to the neuroinflammatory response seen after TBI.

Fatigue is also common in patients suffering from autoimmune and inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus (167-169). It has been hypothesized that inflammatory molecules, such as TNF, IL-6 and C-reactive protein, may contribute to fatigue in rheumatoid arthritis, but there are inconsistent results (170, 171). Cancer patients often experience fatigue during treatment, but also as a problem even long after cure. Inflammation and pro-inflammatory cytokines, hypothalamic-pituitary-adrenal axis dysfunction, and cortisol dysregulation (and its role in regulating inflammation) are postulated mechanisms in the development of fatigue, although no unifying hypothesis has been developed to define fatigue after cancer (172, 173).

Further, myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) is a diagnosis with unknown etiology characterized by a symptom cluster where fatigue is prominent (174, 175). Previous studies have shown inflammation and immune system activation to be the root causes of ME/CFS, such as elevation of cytokines and lymphokines in plasma (176, 177). Also, neuroinflammation detected by positron emission tomography (PET) has been

associated with the severity of the specific neuropsychological symptoms seen in ME/CFS patients (178). Mental fatigue is a central clinical characteristic in stress-related exhaustion disorder, a clinical condition characterized by psychological and physical symptoms of exhaustion developed in response to long-term psychosocial stress (179). A study by Gavelin et al. (180) showed that the structural integrity of the striatum is of relevance for the subjective perception of mental fatigue in stress-related exhaustion disorder.

Hypotheses, models and framework concerning plausible causes of fatigue in neurological illnesses have been proposed. In a review by Penner and Paul (154), a comprehensive review of the literature on fatigue in neurological disease lead to an update on the taxonomy by Kluger et al. (141). The authors listed a range of factors, with special emphasis on cytokine and endocrine abnormalities as well as structural and functional brain changes, assumed to contribute to the subjective experience of fatigue and performance fatigability. The relationship between these factors were illustrated as complex and interdependent. A broad range of factors that may influence fatigue in neurological disorders were also proposed in the empirical framework by Chaudhuri and Behan (136). In summary, it was postulated that metabolic and structural lesions that disrupt the activation in pathways interconnecting the basal ganglia, amygdala, thalamus and frontal cortex are implicated in the pathophysiology of central fatigue. Dobryakova et al. (181) have further developed Chaudhuri and Behan's framework to stress the relationship between the dopamine system and fatigue in MS and other neurological disorders, termed the "dopamine imbalance hypothesis". It was suggested that a disruption of communication between regions in the CNS reliant on dopamine, with either too high or too low levels (the inverted u-shape), plays a key role in the development of fatigue.

As can be seen by the enumeration of disorders listed by Chaudhuri and Behan (136), fatigue is frequent in diseases that show signs of inflammation (aSAH, stroke in general, TBI, PD), autoimmune and autoinflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, MS), and inflammatory disorders (CFS/ME, cancer). All these disorders share some kind of pro-inflammatory cytokine mechanisms, strengthening the hypothesis of cytokine-induced inflammation-mediated fatigue (182) in combination with cumulative evidence that neuroinflammation and pro-inflammatory cytokines plays an important role in neuronal integrity and can lead to persisting alternation in subcortical structures and dopamine function in the brain (94). Hence, dopamine imbalance induced by pro-inflammatory cytokines could be a potential cause of central fatigue (95).

Returning to aSAH, Watson, Ding (183) postulated in a narrative literature review that neuroinflammation as a result of aSAH are likely to contribute to cognitive dysfunction, but its relationship to fatigue was not considered. Despite the considerable aforementioned findings of the plausible role of neuroinflammation in the development of fatigue in a range of disorders, the understanding of fatigue in the relationship between aneurysm rupture and inflammation remain unclear. Further, no definitive biomarkers for fatigue have been identified and the existence of a single biomarker for fatigue seems unlikely.

An exhaustive presentation of all postulated mechanisms and potential interactions between these factors lies outside the scope of the present thesis. Based on the literature presented above, it seems plausible that neuroinflammation and pro-inflammatory cytokines can lead to dysfunction of cortico-subcortical circuits and dopamine function and therefore be of relevance when trying to understand the underpinnings behind post-aSAH fatigue.

1.2.3 Assessment of fatigue

Progress in fatigue research is hampered by issues related to operationalization, but also due to the fact that the phenomenon is difficult to quantify and measure. As Dittner and colleagues (184) points out, there is a "catch-22" situation: "*before a concept can be measured, it must be defined, and before a definition can be agreed, there must exist an instrument for assessing phenomenology*" (p. 166). Consequently, there is no gold standard of fatigue assessment. Fatigue is a subjective experience unique to the individual, and thus the primary method for assessment of fatigue is patient-reported outcome measures (PROMs).

There is limited evidence for the recommendation of any specific PROMs for use within the aSAH population in general, due to the low quality of evidence for the measurement properties (185, 186). The PROMs utilized to specifically capture and measure fatigue are challenged by the same issues. They differ considerably with regard to methodological quality (validated versus non-validated), conceptualization of fatigue (unidimensional versus multidimensional, state versus trait, mental versus physical), assessment focus (frequency, severity or consequences) and sensitivity (generic versus disease-specific) (141, 154). Therefore, choosing the appropriate fatigue PROM is a challenge for both clinicians and researchers (184, 187).

Consequently, there are no validated questionnaires for measuring fatigue specifically after aSAH. The Fatigue Severity Scale (FSS) (188) is one of the most frequently used PROM for assessing fatigue after aSAH (see Table 1) and stroke in general (150), due to its high internal consistency (189). However, the FSS was originally developed for patients with MS and systemic lupus erythematosus to assess fatigue severity and impact. Further, it does not take into consideration the possibility that fatigue might be a multidimensional phenomenon. Also, recent studies of fatigue in neurological disorders have shifted towards a focus on the cognitive and/or mental aspects of fatigue (113, 134, 144, 190-196) following the framework suggested by Chaudhuri and Behan (136). Other questionnaires, like the Mental Fatigue Scale (MFS) (197) and the Multidimensional Fatigue Inventory (MFI) (198) purport to measure the mental aspect of fatigue and are thus more sensitive to aspects of fatigue not directly related to fatigue impact.

As aforementioned definitions of fatigue have classified fatigue as differentiated by domains (subjective or objective) or its presumptive origin (peripheral versus central), it has been conceptualized that fatigue can be directly observed through behavior as performance decrement during sustained mental effort (objective measure of fatigue). However, there is an ongoing debate whether that is the case, thus if mental fatigue and objective performance decline is significantly associated. Therefore, several studies of fatigue have included neuropsychological tests (of cognitive performance) as an attempt to objectively and behaviorally measure fatigue. Even though mental fatigue and cognitive deficits can occur simultaneously, these symptoms are not necessarily closely or significantly related (154, 199, 200).

Few studies can point to a statistical association between subjective fatigue and objective performance decrement, with maybe some exceptions in patients with MS and TBI (201, 202). For the TBI population, it has been suggested that inconsistencies in the link between subjective fatigue and objective (cognitive) performance can be enlightened by the “coping hypothesis” (203). It has been postulated that TBI patients need to compensate for cognitive deficits by extra mental effort that ultimately results in fatigue. Although the cognitive performance can be comparable to the level of healthy controls, the compensatory effort causes fatigue. Thus, empirical evidence regarding assessment of fatigue through behavior have yielded conflicting results.

1.2.4 Treatment of fatigue

To the author's knowledge, only a single RCT from 1998 (204) has aimed, albeit only partially, at therapeutic intervention for the treatment of post-aSAH fatigue. Further, systematic reviews (205, 206) on treatments of post-stroke fatigue are inconclusive; there is insufficient evidence on the efficacy of both behavioral and pharmacological treatment strategies. Even though there is no evidence-based treatment for post-aSAH fatigue that yet can be recommended, several studies of fatigue interventions have shown promising results. Since fatigue may have several causative, mediating or maintaining factors, a number of potential treatment strategies may be helpful to alleviate or reduce fatigue symptom burden.

1.2.4.1 Non-pharmacological treatment of fatigue

Non-pharmacological intervention studies intended to treat fatigue after aSAH are nonexistent. Also, a recent systematic review and network meta-analysis of non-pharmacological interventions for post-stroke fatigue (206), comprising 777 stroke patients, found that most interventions did not significantly differ in effectiveness when compared. However, it was indicated that the best non-pharmacological intervention for post-stroke fatigue was Community Health Management (i.e., interdisciplinary rehabilitation consultations), followed by Traditional Chinese Medicine (i.e., treatment with heat and acupuncture) and Cognitive Behavioral Therapy (CBT).

Since there is limited evidence to support any non-pharmacological intervention for fatigue after aSAH and stroke in general, studies regarding other relevant neurological disorders will be presented. Non-pharmacological interventions of fatigue can broadly be divided into the categories psychotherapy (i.e. CBT or mindfulness) and education/symptom management (also including interdisciplinary rehabilitation treatment).

A systematic review and meta-analysis by van den Akker et al. (207) has lend support to the effectiveness of CBT treatment for managing fatigue in MS patients. In a more recent systematic review and meta-analysis, Phyo et al. (208) also found CBT to be associated with reduced fatigue. Two RCTs found CBT, received in either group sessions or individual, effective in reducing fatigue in rheumatoid arthritis patients (209, 210). A systematic review

on the use of non-pharmacological interventions in the treatment of fatigue for cancer showed a convergence in favor of CBT, but also physical activity and educational interventions, with levels of evidence ranging from moderate to high (211). It is also plausible that CBT is effective for patients suffering from fatigue after TBI, yet the evidence so far is mixed (212).

A systematic review and meta-analysis on the utility of mindfulness training in the treatment of fatigue after stroke, TBI and MS concluded that mindfulness-based interventions might relieve fatigue, but with a moderate effect size (213). Support for this conclusion was found in similar and recent studies for patients after mild TBI (214) and with MS (215). It has also been promising results for mindfulness-based interventions on fatigue in cancer survivors (211, 216), although the effect in this patient population has been deemed tentative (217) or equivocal (218) by others.

Reviews and meta-analyses for the efficacy of education interventions have found that for MS patients, education (energy conservation treatment) can be more effective than no treatment in reducing the impact of fatigue in the short term (219). Education can also have a stronger and more significant effect on reducing the impact or severity of MS-related fatigue compared to medication (Amantadine and Modafinil) (220). It has also been shown that educational program and especially CBT-based approaches had a positive effect on reducing fatigue for MS patients, but not for depression (221). It was also concluded in a more recent review that fatigue self-management intervention that incorporated educational materials seemed optimal for reducing the negative effects of cognitive fatigue in MS patients (222), but further stated that there was not sufficient evidence for a clear recommendation about effective fatigue management. Interventions employing an individual approach also seemed to reduce fatigue more effectively than group-based approaches. This lends supports to the preliminary results by Ghahari and Packer (223) that suggest a face-to-face self-management program to be more effective in decreasing fatigue compared to online deliverance for adults with neurological conditions (223). Apart from CBT, a Cochrane review (224) demonstrated that psychosocial interventions mainly involving education had a small beneficial effect upon fatigue in patients with rheumatoid arthritis.

A common denominator for all the studies mentioned above is methodological issues: Wide-ranging heterogeneity in study design, sample, and measures used to assess outcomes renders it difficult to evaluate the efficacy of format or elements aimed at reduction of fatigue in different neurological populations. Furthermore, the optimum time to intervene is unclear.

Even though the effect seems to be modest, CBT and educational interventions may improve fatigue severity or intensity in a range of disorders presenting with fatigue. However, it has also been stated that non-pharmacological treatment does not ameliorate fatigue per se, but improves psychosocial function (136).

1.2.4.2 Pharmacological treatment of fatigue

Pharmacological interventions of fatigue can broadly be divided into the categories of CNS stimulants (Methylphenidate, Modafinil) and antidepressants (most commonly Selective Serotonin Reuptake Inhibitors), with experimental compounds labeled neuroprotective agent (tirilazad mesylate) and dopamine stabilizer ((−)-OSU6162).

As mentioned above, one pharmacological intervention study has been performed in the aSAH population. Ogden et al. (204) randomized 31 women at admission for SAH and assessed the efficacy of tirilazad mesylate (150 mg/100 mL), a hypothesized neuroprotective agent, compared to placebo (100 mL) for 10 consecutive days. After three months, 18 participant completed assessment and the presence of debilitating fatigue was indicated as 'yes' or 'no' based on the subjective opinion of the interviewer. The study found no effect of tirilazad mesylate on fatigue after SAH. However, the study was primarily intended to test the feasibility of the intervention rather than to investigate efficacy, did not have fatigue as primary outcome measure nor inclusion criteria, had a small sample size and used available-case analysis that has a high risk of attrition bias. A Cochrane review from 2001 (225) stated that tirilazad has no role in the clinical treatment of stroke.

Methylphenidate (Ritalin)**,** a CNS amphetamine-like stimulant, is a neuroenhancer that blocks reuptake of dopamine and norepinephrine and increases extracellular dopamine in the striatum, nucleus accumbens, and prefrontal cortex (226, 227). Studies evaluating the benefits of methylphenidate in treating fatigue after TBI (212, 228-232) and in PD (233) have been positive, but the results are either inconclusive for cancer patients (234) or negative for MS patients (235, 236).

Modafinil, an atypical dopamine reuptake inhibitor of presynaptic dopamine transporter, is also labeled a neuroenhancer (227). Its pharmacological actions seems to be similar to stimulants even though the mechanisms of actions is not fully understood (237). A systematic

review and meta-analysis found no support for Modafinil in the treatment for fatigue in MS patients (238). This was further supported by a recently published randomized, placebo-controlled, crossover, double-blind trial assessing the efficacy of Modafinil, Methylphenidate and Amantadine for MS-fatigue (235), in which none of the commonly prescribed medications were superior to placebo in improving MS-related fatigue. Modafinil after TBI seems unlikely to be effective (239), where the results have been reported as mixed (212).

Fluoxetine is one of the oldest selective serotonin reuptake inhibitors (SSRIs) with a well-known safety profile (227). Choi-Kwon et al. (240) performed a double-blinded, randomized, placebo-controlled study assessing the efficacy of fluoxetine on fatigue after ischemic and hemorrhagic stroke. They found no difference between the treatment and placebo group regarding number of patients with fatigue or percent changes in fatigue scores 3 and 6 months after treatment, but an overall effect of fluoxetine on emotional incontinence and depression symptoms. They conclude that fluoxetine does not alleviate post-stroke fatigue and that post-stroke fatigue is not closely related to serotonergic dysfunction. In the most recent Cochrane review of SSRIs for stroke recovery (241), it was stated that there is no reliable evidence that SSRIs should be used routinely to promote recovery after stroke. In this review, 32 trials reported the effect of fluoxetine. However, only one of the high-quality trials (242) assessed fatigue, finding that fluoxetine given daily for 6 months after acute stroke reduced the occurrence of depression, but did not alleviate fatigue. Further, Dimitrios et al. found that antidepressants (Duloxetine, Citalopram and Sertraline) improved symptoms of depression and anxiety, but not fatigue, in patients with poststroke depression. Altogether, these studies implicates that there is no beneficial effect of antidepressant for post-stroke fatigue (205).

The development of pharmacological interventions, aiming at achieving high precision neurotransmitter signaling, in order to diminish mental fatigue is of utmost importance. One approach for pharmacological treatment of mental fatigue would be to restore or “stabilize” one or several signaling systems in the brain, such as the dopaminergic system, which is widespread and of great importance for cognition, behavior and motor functions. If the dysfunction in one neurotransmitter system was to be restored, a cascade of restoration in other signal systems may result, thereby creating prerequisites for improved brain functions. Thus, there is a need for more robust RCTs to evaluate the efficacy of both previously tried pharmacological treatments with promising results and experimental compounds.

1.2.4.3 (−)-OSU6162

During the early eighties, a research team under Professor Arvid Carlsson at the Department of Pharmacology, University of Gothenburg, discovered a central dopamine receptor agonist called 3-(3-hydroxyphenyl)-N-n-propyl-piperidine, 3-PPP (243). The two enantiomers of 3-PPP were evaluated, and it was shown that the negative enantiomer (−)-3-PPP activated dopamine autoreceptors and also acted concomitantly as an agonist at postsynaptic dopamine site (244). Further research effort continued, since the effect of (−)-3-PPP faded rather quickly and therefore was unsuitable for clinical use. This lead to the development of a substituted (S)-3-phenylpiperidine derivative [(*S*)- (−)-3-methylsulfonylphenyl-1-propylpiperidine], called (−)-OSU6162, which was found to exhibit a normalizing profile on psychomotor activity by a combination of stimulatory and inhibitory effects (245, 246).

(−)-OSU6162 is a compound classified as a monoaminergic stabilizer with an affinity to mainly D2 and D3 receptors (247), corroborated by the results of a PET study in 2015 (248). Conceptually it is a drug that normalizes dopaminergic signaling both in the case of excessive and deficient dopaminergic tone, thus a dopaminergic stabilizer (249). The position of the peak will inter alia depend on individual pharmacokinetics. It has also been proposed that (−)-OSU6162 exerts stabilizing effects on serotonergic transmission, for instance via a partial agnostic action on 5-HT2a receptors (250, 251).

In experimental and preliminary trials, short-term studies have documented (−)-OSU6162 to be effective antidyskinetic and antipsychotic. It was found to inhibit L-DOPA-induced dyskinesia in a dose-dependent manner in animal models of PD, without interference with the therapeutic effect of L-DOPA (252, 253). It has also been shown to have an impact on both positive and negative symptoms in patients with schizophrenia (254, 255). Further, the compound might attenuate alcohol use in animals (256, 257) and humans (258).

To this date, approximately 250 patients have been included in clinical trials evaluating the efficacy of (−)-OSU6162 in the treatment of fatigue (259-265). The majority of patients have been treated with oral doses ranging from 10–90 mg/day in total. Two studies by Haghighi and colleagues (262, 265) employed an open-label, single-arm design with a treatment duration of 12 weeks with oral doses ranging from 30-90 mg/day in total. In patients with MS (262), improvements were observed with respect to fatigue (measured with the Mental Fatigue Scale), depressive symptoms (Beck Depression Inventory) and several aspect

regarding health-related quality of life (SF-36). In patients with ME/CFS (265), improvements were seen on the same outcome measures mentioned in the previous study, but also on the FSS. The authors discussed the possibility of the MFS to be a more sensitive tool than the validated FSS for detecting clinical improvement of mental fatigue. Both studies reported that (−)-OSU6162 was safe and well tolerated with a remarkably mild adverse event profile. However, it should be noted that there was no significant correlation between (−)-OSU6162 plasma concentration and scores obtained in the clinical ratings for both studies.

Three studies evaluating the efficacy of (−)-OSU6162 employed a randomized cross-over, double blind and placebo-controlled design with a 4+4 weeks treatment period excluding washout in-between periods (259, 260, 264). Johansson et al. (259) included patients suffering from mental fatigue after stroke and TBI, where they found a significant improvement on the primary endpoint, the MFS, with no effect of diagnosis (stroke vs. TBI). No significant effects were detected for the secondary endpoints, i.e. the neuropsychological tests, subscales for depression and anxiety (Comprehensive Psychopathological Rating Scale) and daily activity (Frenchay Activity Index). This study did not measure (−)-OSU6162 plasma concentration. Nilsson et al. (264) replicated the former study (170), but included more than twice the number of TBI and stroke participants (n=30). They did not find a statstical treatment effect of (−)-OSU6162 with respect to mental fatigue (MFS) in general, but a subgroup of patients on the highest level of sick leave (50-100% versus <50%) showed improvements on the MFS during the period of (−)-OSU6162 treatment. Further, an effect on patients' activity level (FAI total scores and subscale FAI outdoor scores) was found for (−)-OSU6162. Further, (−)-OSU6162 plasma concentration and change in MFS total score did not correlate. However, the authors noted that visual inspection of scatter plots indicated a shift in response when concentration exceeded 0.8 µM (i.e., the inverted U-shaped dose-response curve). Further, the authors discussed the possibility of differences in dosage and degree of placebo response possibly related to the difference in MFS and FAI scores in the two latter studies. Kloberg et al. (260) included 15 participants with Huntington's disease (HD) and found that (−)-OSU6162 treatment significantly improved vitality/energy (SF-36) and depressive symptoms (Beck Depression Inventory). This study did not measure (−)-OSU6162 plasma concentration. All three studies stated that (−)-OSU6162 was well tolerated (profile of adverse reactions). Further, all made statements about the potential limitation with respect to interepretation of results due to possibly carry-over effects.

Two studies (261, 263) employed a randomized, double-blind, placebo-controlled design to investigate the efficacy of (−)-OSU6162 on fatigue. Berginström et al. (261) randomized 64 participants with TBI to treatment (n=33) or placebo (n=31) with a stepwise increase of dose to maximum 30 mg/day in total over a 4 week period. Results showed that (−)-OSU6162 had no significant effect on mental fatigue or neuropsychological test performance, but both groups showed significant improvement on the FSS and MFS and partially on the cognitive tests. The latter was interpreted as test-retest effects, but the former was linked to a placebo effect. Plasma concentrations of (−)-OSU6162 were lower than expected (average concentration, 0.14 μM) and did not correlate with any of the outcome measures except for a negative association with the Verbal Fluency Category-Switching. Nilsson et al. (263) randomized 62 patients with ME/CFS to placebo or (−)-OSU6162 with a stepwise increase of dose to maximum 30 mg/day in total over a 2 week period. A significant improvement was observed for mental fatigue (MFS) and the clinical global impression of change (CGI-C) scale, but for both groups. The authors stated that the placebo response can be linked to expectation-related improvement and dopamine release, hence studies comparing (−)-OSU6162 with placebo are dealing with mechanisms involving the dopamine system for both the investigational medical product and the comparator. The effect of (−)-OSU6162 was found to be superior in the subgroup of ME patients who used concomitant pharmacological treatment for depression. Antidepressant effects of (−)-OSU6162 was also observed in Huntington's disease patients (260). Moreover, there was a significant correlation between (−)-OSU6162 and clinical improvement (measured with MFS, FibroFatigue scale, and BDI), hence interpreted to be in favor of a pharmacological effect. Both studies found (−)-OSU6162 to be safe and well tolerated.

Concluding remarks

There is limited knowledge about the mechanisms of fatigue where also the cause-effect relationship of these mechanisms are undetermined. Culminating evidence implicate the involvement of neuroinflammation, dysfunction of cortico-subcortical circuits, and dopamine function alterations in the development of fatigue. Nevertheless, status quo is that there is no clear recommendation about effective treatment of fatigue. When taking into account the high incidence of aSAH during mid-life in combination with an apparently high frequency of post-

aSAH fatigue, finding an evidence-based treatment for fatigue is not only of economical and psychosocial importance for the individual, but also for the society as a whole.

The challenges regarding correct operationalization, proper assessment and adequate knowledge about the pathophysiological underpinning of fatigue in the search of an effective cure is not limited to the aSAH population. However, the literature on fatigue after aSAH is scarce compared to other neurological illnesses, especially MS. With only one trial partially exploring a pharmacological intervention for fatigue after aSAH, there is an obvious need for more research on treatment interventions that have the potential to alleviate post-aSAH fatigue. The novel compound (−)-OSU6162 seems like a promising candidate.

2 Main objectives and research questions

The overall aim of the present thesis was to expand the knowledge about the phenomenology and underlying mechanisms behind fatigue after aSAH, and achieve a better understanding of how fatigue after aSAH may be assessed and treated. The specific research questions of the three included papers were as follows.

Paper I

1. Is fatigue a frequent and long-lasting symptom after aSAH?
2. Are factors in regards to management and complications of aSAH predictive for the development of fatigue after aSAH?
3. If so, are the significant predictors indicative of higher severity of hemorrhage and consequently more complications?

Paper II

4. What are the prominent features of fatigue after aSAH?
5. Is fatigue after aSAH distinct from emotional problems, such as depression and anxiety?

6. Is fatigue after aSAH a subjective experience not related to objective performance fatigability as measured with neuropsychological tests?
7. Is fatigue after aSAH related to HRQoL and ability to return to work?

Paper III

8. Is (−)-OSU6162 superior to placebo in the treatment of fatigue after aSAH?
9. Is (−)-OSU6162 superior to placebo in the treatment of other common sequelae after aSAH?
10. Is plasma concentration of (−)-OSU6162 associated with clinical improvement (as measured on both primary and secondary endpoints)?

3 Materials and methods

3.1 Study design

The thesis is based on a phase II, double-blind, randomized, placebo-controlled study design to evaluate the effect of (−)-OSU6162 in the treatment of fatigue after aSAH. Data was acquired consecutively in a cross-sectional cohort design in order to recruit patients and conduct a baseline assessment in the RCT as summarized in paper I and II, respectively. The results of the RCT are presented in paper III. Figure 4 shows the study design for each paper in the thesis.

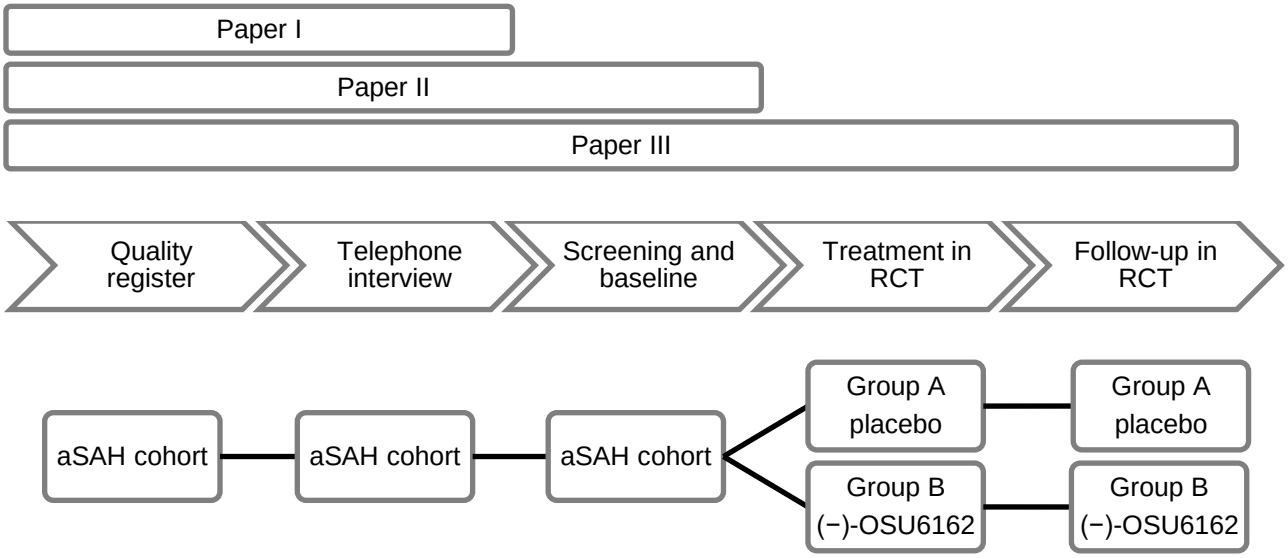

Figure 4. Study design.

3.2 Study population

The thesis is based on a cohort of patients treated at Oslo University Hospital (OUH) for aneurysmal subarachnoid hemorrhage in the period between January 2012 and March 2018. All aSAH survivors were recruited from the South-Eastern Norway Regional Health Authority, serving a population base of 3.1 million people as of 2020, more than half of the total population in Norway. The names of the aSAH patients and data on their medical admission and clinical course were obtained from medical journals and the institutional quality register at the Department of Neurosurgery (DNS), OUH. Recruitment and data acquisition for this thesis lasted from July 2017 to September 2019, and was conducted at the Department of Physical Medicine and Rehabilitation (DPMR), OUH.

3.3 Recruitment

For paper I, patients treated for aSAH between January 2012 and December 2017 were contacted. In paper II and III, 23 patients treated for aSAH between January 2018 and March 2018 were added to the recruitment process.

3.3.1 Inclusion and exclusion criteria in paper I

The study population consisted of patients that had suffered aSAH at least 1 year earlier, were 18 years of age or older, and lived permanently in the South-Eastern Norway RHA at the time of assessment. We excluded patients who were residents in nursing homes and/or were deemed cognitively too debilitated to consent and/or complete the telephone interview, as well as patients who were not fluent enough in Norwegian to be able to answer the questions in a valid manner.

3.3.2 Inclusion and exclusion criteria in paper II and III

The study population consisted of aSAH patients that underwent prescreening by telephone interview (see also inclusion and exclusion criteria under section 3.3.1). For participation in the RCT study, all of the following inclusion criteria had also to be fulfilled:

- The presence of fatigue, based on mean score of ≥4 on the questionnaire Fatigue Severity Scale (FSS) at prescreening and clinical signs of fatigue at screening, at ≥12 months after hemorrhage
- ≥ 18 years at inclusion
- Post-menopausal (women) or using adequate contraceptive measures

Further, patients were excluded from participation in the RCT study if they met any of the following exclusion criteria:

- Residual symptoms following other pathologies than aSAH
- Diagnosed with current epilepsy, neurodegenerative disease, cerebral paresis, tumor cerebri, cerebral arterio-venous malformations
- Inadequately treated hydrocephalus
- Patients that have undergone brain surgery, have been hospitalized for head trauma, or suffered intracranial hemorrhage, stroke, or infectious brain diseases within the last 12 months
- Clinically significant liver and renal disease

- For women of childbearing age not using contraceptives, current pregnancy or breast-feeding, or intention to become pregnant within 3 months after the last dose
- Pathologic electrocardiography, as assessed by the investigator, with prolonged QTc interval (>480 msec.)
- Clinically significant blood test deviations
- Active substance abuse (drug screen taken at screening visit: Amphetamines, Barbiturates, Benzodiazepines, Cocaine, Opiates)
- Previous treatment with (−)-OSU6162
- Patients using metabolic enzyme inhibitors and those using drugs with a narrow therapeutic window or requiring individual dose adjustments. The following Anatomical Therapeutic Chemical (ATC) Classification System categories were not allowed: N06B A+X, N07A, N06A G+X, N05A, N03A, J04A, J01D H, L04A D, B01A A, C01A A, H01B A and N04B D.
- Any surgical or medical condition which, in the opinion of the investigator, might interfere with the absorption, distribution, metabolism or excretion of (−)-OSU6162
- Use of acute or chronic medications for other medical conditions was allowed based on the investigator's judgement. Occasional use of over-the-counter (OTC) medication was not allowed during the study or one month prior to inclusion, whereas regular, prescribed OTC medication use was allowed if stable over time.
- Any reason why, in the opinion of the investigator, the patient should not participate.

3.4 Procedure

Prescreening via telephone was conducted by the PhD candidate (clinical neuropsychologist). All patients were informed about the purpose of the study and gave oral consent before any questions were asked. Patients were assessed with the Fatigue Severity Scale (for specification of items, see section 3.6.2). Questions regarding demographics, concomitant medications, and both prior and current health status (medical, surgical and psychiatric) were also asked. In the appendix (section 8.2), the prescreening form is described in detail. Patients deemed eligible after prescreening received the written consent form by post when invited to visit DPMR at OUH for further screening.

At the beginning of the RCT during the first visit at OUH, all patients received written and oral information about the purpose of the study, its procedures and any risks involved with participation from the principal investigator (M.D, PhD) or team physician investigator (M.D, PhD). All patients signed informed consent before any procedures took place. An electronic data capture was used by both team investigators (Viedoc Clinic) and patients (ViedocMe) to register data subsequently.

Patients underwent an initial consultation with a team physician investigator where they were asked questions regarding inclusion and exclusion criteria, demographics, medical and surgical history, and concomitant medications. Blood and urine samples, including drug screen and pregnancy tests for fertile women, were collected. Further, patients went through physical and neurological examinations, electrocardiography, registration of height and weight, and vital sign assessment.

Patients filled out PROMs where the mode of administration primarily was electronic (ViedocMe on computer, tablet or mobile phone), but were able to opt for paper based PROMs if the former was viewed as unfeasible by the patient. By using ViedocMe, the possibility of missing data was reduced to a minimum (see description in appendix, section 8.3). All patients also completed neuropsychological testing. Training in how to answer PROMs (electronically/paper) and neuropsychological testing was administrated by the PhD candidate (clinical neuropsychologist) with the help from a team psychologist investigator (clinical neuropsychologist, PhD) when necessary.

After the initial screening process, the team physician investigator performed a review of the exclusion criteria and concomitant medications. If no contradictions to the inclusion and exclusion criteria appeared, the patient was randomized to start treatment with (−)-OSU6162 or placebo. With a prescription from the team physician investigator, the patient picked up six containers each filled with 60 tablets from the Hospital Pharmacy at OUH.

All patients underwent assessment of efficacy (both primary and secondary outcome measures), safety and tolerability at different points of time during and after treatment. Unscheduled visits were also possible in order to regulate doses, because of adverse events (AEs) or at the request of a participant. Patients returned the remaining tablets at week 12 (the end of treatment). The timing of all scheduled study events is shown in a flow chart as illustrated in Table 2.

Table 2. Flow chart of scheduled procedures in the RCT.

	Scr.	**Treatment**					**Follow-up**	
		Start				**End**		
Visit number	**1**	**2**	**3**	**4[1]**	**5**	**6**	**7[1]**	**8**
Week	**-2**	**0**	**1**	**4**	**8**	**12**	**15**	**20**
Visit window (days)	-14/-5		+/-3	+/-3	+/-3	+/-3	+/-3	+/-7
Informed consent	X							
Inclusion/Exclusion criteria[2]	X	X[3]						
Randomization		X						
Blood sample	X[4]				X[4 5]	X[4 5]		
Urine sample	X[6 7 8]	X[7]		X[7]	X[7 8]	X[7 8]	(X)[7]	
Examination		X			X	X		X
Heigh and weight		X[9]	X		X	X		X
ECG		X	X		X	X		X
Vital signs		X	X		X	X		X
PROMs	X		X[10]	X	X[10]	X		X
NP testing	X					X		
Drug administration		X	X[11]	X[11]	X[11]			
Drug compliance			X		X	X		
Concomitant medication	X	X	X	X	X	X		
Adverse events			X	X	X	X		X

Abbreviations: Screening = Scr.; Physical and neurological examination = Examination; Electrocardiography = ECG; Patient-reported outcome measures = PROMs; Neuropsychological testing = NP testing

[1] Telephone interview
[2] Including demographics, medical history and diagnosis
[3] Re-check eligibility criteria
[4] Clinical chemistry and hematology
[5] Plasma concentration of (-)-OSU6162 taken only once, at either week 8 (preferably) or week 12
[6] Drug screen on site
[7] Pregnancy test only for fertile women
[8] Urine analysis
[9] Height only at baseline
[10] Only Fatigue Severity Scale (FSS)
[11] Increase in drug dose at week 1, 4 *or* 8 if lack of response

3.5 Treatment

(−)-OSU6162 was defined as the Investigational Medicinal Product (IMP), which also included placebo. The active ingredient of (−)-OSU6162 is the S-enantiomer with the chemical name (S)-3-[3-(methylsulfonylphenyl]-1-propylpiperidine hydrochloride. (−)-OSU6162 and placebo tablets of 15 mg had identical appearance (white, circular, coated) to ensure double blinding. The composition of the IMP is listed in Table 3.

Table 3. Ingredients in IMP

Name of Ingredient	**Quantity** (mg/unit)	**Function**
Active Substance		
(−)-OSU6162	15	Drug substance
Excipients		
Cellulose, microcrystalline (Avicel PH-200)	49.6	Filler
Lactose monohydrate (SuperTab30GR)	146.8	Filler
Croscarmellose Sodium (Ac-Di-Sol)	12.64	Disintegrant
Magnesium stearate	3.78	Lubricant
Opadry II	12	Film coating system
Target	242	-

At visit 1, patients were assigned a screening number. If all eligibility criteria were fulfilled at the end of visit 2, the patients was assigned to treatment with either IMP or placebo in a 1:1 ratio in accordance with the randomization list administered by The Clinical Trial Unit, Research Support Services, Oslo Hospital Services Division. The IMP was produced, packed, and labeled by the manufacturer Galenica AB, Lund, Sweden and shipped to the Hospital Pharmacy at OUH where the patient picked up the IMP with the prescription handed to them from the team physician investigator (at the end of visit 2). The IMP was dispensed into 30 mL twist-off containers each filled with 60 tablets and labelled according to the randomization list (see Figure 5). The IMP for each patient were six containers in total.

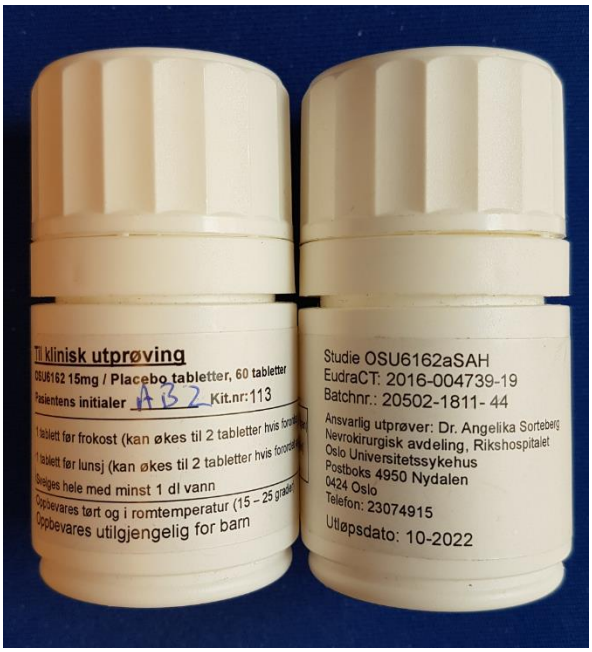

Figure 5. Two containers filled with 60 tablets each. The picture illustrates the vials and the label layout used in the RCT. Photo by Angelika Sorteberg.

All patients received a dose of IMP 15 mg BID instructed to be taken twice a day, before breakfast and lunch. The duration of treatment was 12 weeks. An increase of dosage to maximum 30 mg BID x 2 was considered after 1 week if there was a lack of response to treatment, determined by interview and an improvement of less than 1.5 points on the Fatigue Severity Scale (FSS). An increase of dose could be postponed to week 4 or 8, but only increased once. If the dose of 30 mg BID x 2 was not tolerated, the patient returned to initial dose of 15 mg BID x 2.

3.6 Measures and assessment

The assessment of prevalence and predictors of fatigue after aSAH (paper I) was performed by comparing demographics, as well as medical and radiological data obtained during management for aSAH, between patients with and without fatigue (Fatigue Severity Scale mean score ≥4 versus <4, respectively) in the chronic phase. For investigation of clinical characteristics and associated factors of fatigue after aSAH (paper II), we used results from PROMs and neuropsychological test performances obtained during screening and baseline

assessment of the RCT study. The assessment of efficacy in the RCT study (paper III), was performed by comparing the results from PROMs and neuropsychological test performances at baseline and at different points of time during and after treatment.

3.6.1 Sociodemographic information and aSAH-related characteristics

Demographic and clinical information were obtained from medical journals, the institutional quality register at the DNS, OUH, structured interviews and/or clinical examination at screening/baseline. A more detailed description of how data on condition at admission and clinical course during the management of aSAH were categorized can be found in paper I. However, an overview of sociodemographic and aSAH-related factors for papers I-III are provided in Table 4.

Table 4. Overview of collected sociodemographic and aSAH-related factors (papers I-III).

	Paper I	Paper II	Paper III
Sociodemographic information			
Age	X	X	X
Sex	X	X	X
Education		X	(X)
aSAH-related characteristics			
Time since ictus	X	X	X
Nicotine use at ictus	X		
Aneurysm localization	X	X	(X)
Aneurysm repair method	X	X	(X)
Hunt and Hess (HH, (41)	X	X	(X)
Glasgow Coma Score (GCS, (42)	X		
Loss of consciousness at ictus (LOCi)	X		
Rebleed before aneurysm repair	X		
Amount of subarachnoid blood (modified Fisher, (37)	X		
Amount of intraventricular blood (modified LeRoux, (38)	X		
Intracerebral hemorrhage	X		
New cerebral infarction	X	X	X
Acute hydrocephalus (need of external drainage of CSF)	X	X	(X)
Chronic hydrocephalus (implanted shunt)	X	X	(X)
Severe vasospasm	X		
Clinical and functional outcome			
Body mass index (BMI, kg/m²) and/or change in BMI		X	X
Clinical outcome (modified Rankin Scale, mRS)		X	X
Neurological status (NIHSS)		X	(X)
Return to work (RTW)		X	X

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; (X) = same cohort in paper II-III.

3.6.2 Patient-reported outcome measures (PROMs)

The PROMS utilized were selected based on the need for exploring multiple facets of fatigue and detection of changes in impact on emotional function and perceived quality of life – factors know to have a high incidence after aSAH and associated with fatigue. Answering all PROMs took approximately 60 to 90 minutes and PROMS employed in the RCT (paper II-III) were as followed:

3.6.2.1 Fatigue

Based on the assumption on fatigue being a multidimensional construct, we used two PROMs to capture different aspects of fatigue. The Fatigue Severity Scale (FSS) (188) is one of the best known and most frequently used questionnaires for evaluating fatigue in aSAH and stroke studies in general (266) with good psychometric properties (184). It has been shown to be sensitive enough to detect change over time as an outcome measure in clinical studies (187). The FSS is mainly focused on the impact of fatigue on physical functioning and everyday life rather than the intensity of fatigue symptom as the name implies. It is classified as a unidimensional scale (184). We used the Norwegian version of the FSS (111). The nine items of the FSS questionnaire are denoted: 1) My motivation is lower when I am fatigued, 2) Exercise brings on my fatigue, 3) I am easily fatigued, 4) Fatigue interferes with my physical functioning, 5) Fatigue causes frequent problems for me, 6) My fatigue prevents sustained physical functioning, 7) Fatigue interferes with carrying out certain duties and responsibilities, 8) Fatigue is among my three most disabling symptoms and 9) Fatigue interferes with my work, family, or social life. The FSS score is the mean of the nine item scores. A mean FSS score of ≥ 4 is considered indicative of fatigue (Krupp et al., 1989). In this thesis, FSS was the only PROM also used in paper I for assessing prevalence of fatigue.

Although new and of limited use in the aSAH population, we also added the Mental Fatigue Scale (MFS) (197) to capture mental fatigue features and related symptoms. The MFS questionnaire comprises 15 questions regarding affective, cognitive and sensory symptoms related to fatigue. The 15 items of the MFS questionnaire are: 1) Fatigue in general, 2) Lack of initiative, 3) Mental fatigue, 4) Mental recovery, 5) Concentration difficulties, 6) Memory

problems, 7) Slowness of thinking, 8) Sensitivity to stress, 9) Emotional instability, 10) Irritability, 11) Sensitivity to light, 12) Sensitivity to noise, 13) Decreased sleep, 14) Increased sleep and 15) 24-hour variations. Items 1-14 are scored on a scale ranging from 0 to 3; where 0 corresponds to normal function, 1 indicates a problem, 2 indicates a pronounced problem and 3 a maximal problem. The patient can also choose an answer in between the exemplified alternatives; i.e. 0.5, 1.5, and 2.5. Item 15, which is not included in the total sum score, indicates which time of the day is felt best and worst if there is a diurnal variation. A MFS sum score of ≥10.5 is suggestive of mental fatigue (267).

A prior history of fatigue was registered by checking medical records and by asking the patient: ‘‘did you experience fatigue before your aSAH’’ (yes/no). If the patient answered yes, they were encouraged to describe, regardless of cause, the nature of their pre-ictal fatigue. Pre-ictal fatigue with an intensity and severity that caused problems in daily life were defined as “fatigue before aSAH” (140).

3.6.2.2 Mood disorders

Beck Depression Inventory 2nd edition (BDI-II) (268) and Beck Anxiety Inventory (BAI) (269), was included to assess the frequency and severity of depressive and anxiety symptoms during the past 2 weeks, respectively. Both scales are self-report questionnaires with 21 items each rated on a 4-point scale from 0 to 3. Higher scores indicate more severe symptomatology, where BDI-II score of ≥20 was categorized as clinical depression (moderate to severe depressive symptoms) and BAI score of ≥16 was categorized as clinical anxiety (moderate to severe anxiety symptoms). We chose a conservative cut-off for symptoms to be regarded as clinically relevant to reduce the rate of false positives, since there is a potential for symptom overlap between fatigue and emotional problems. Further, mood disorder was defined as the presence of clinical depression and/or clinical anxiety.

A prior history of depression and anxiety was registered by checking medical records and by asking the patient: “did you experience psychiatric problems before your aSAH” (yes/no). If the patient answered yes, they were encouraged to describe the nature of the symptoms, severity and duration. Those who reported depressive and/or anxiety symptoms, often in combination with psychotherapy or pharmacological treatment, interfering with activities of daily life, were defined as having depression or anxiety before aSAH.

3.6.2.3 Health-Related Quality of Life

Short Form Health Survey, 36-item (SF-36) (270), one of the most frequently used questionnaire for measurement of HRQoL in the literature, was also added. It is a 36-item self-report questionnaire measuring perceived HRQoL in eight different health-related domains: physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. (271).

3.6.3 Neuropsychological tests

The selection of neuropsychological tests chosen for this study was from a pragmatic approach after an internal discussion of the advantages as well as drawbacks of available tests also in consideration of previous literature about typical cognitive deficits after aSAH. Completion of the neuropsychological test battery took approximately 90 minutes (including a 15 minutes break). All participants underwent testing before randomization and right before the end of treatment in the following order:

- Grooved Pegboard (Halstead-Reitan Neuropsychological Battery) (272), a test of fine sensomotor finger dexterity.
- The California Verbal Learning Test – Second edition (CVLT-II) (273) Standard version at Visit 1 and Alternative version at Visit 6, a test of verbal learning and memory.
- Conners' Continuous Performance - 3rd edition (CPT-III) (274) captures different aspects of attention: Inattentiveness, impulsivity, sustained attention and vigilance.
- Digit Span from Wechsler Adult Intelligence Scale – fourth edition (WAIS-IV) (275), a test of auditory attention and working memory.
- Trail Making Test from Delis-Kaplan Executive Function System (D-KEFS) (276), where the five trials measures different aspects of visual attention and scanning abilities, processing speed and cognitive flexibility.
- Color-Word Interference Test from Delis-Kaplan Executive Function System (D-KEFS) (276), where the four trials measures different aspects of word finding capacity, processing speed, inhibition and cognitive flexibility.

3.6.4 Safety and tolerability assessment

A range of safety measures were implemented in the RCT study where the points of time for the different assessments are previously illustrated in a flow chart (see Table 2):

- Adverse events (AEs): Any untoward medical occurrences in a patient which did not necessarily have a causal relationship with the treatment was recorded as an AE and was evaluated continuously from first week of treatment and to the end of study.
- Physical and neurological examinations: All patients underwent standard physical (including weight) and neurological examinations; see detailed description of the procedure in section 8.1.
- Vital signs: Supine systolic and diastolic blood pressure (mmHg) and supine pulse/heart rate (beats per minute) were monitored after lying down for 5 minutes. Values for blood pressure and pulse/heart rate were assessed as normal, abnormal not clinically significant or abnormal clinically significant.
- Electrocardiograms: A standard 12-lead electrocardiogram and the QT interval measured. The electrocardiography was recorded 1-2 hours after intake of the IMP/placebo during active treatment. The corrected QT interval (QTc) was noted as "QTc interval change from baseline <60 ms" (yes/no) and "QTc interval >500 ms" (yes/no). Discontinuation was warranted if any of the measurements were to be answered yes.
- Clinical laboratory safety tests: Clinical chemistry (C-reactive proteine, Calcium, Potassium, Sodium, Gamma-Glutamyl-Transferase, Glucose, Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Creatinine, Total bilirubin, Thyroid stimulating hormone, free thyroxine, and Prolactine), hematology (Sedimentation response, hemoglobuline, platelet count, and white blood cell count) and urine analysis (Glucose, leucocytes, and nitrite). The observed values were recorded in Viedoc Clinic as "normal", "abnormal not clinically significant" or "abnormal clinically significant".
- Pregnancy test: Child bearing potential was established by interview and baseline blood tests with follicle stimulation hormone levels. In fertile women, a pregnancy test at start and every month during treatment and within 30 days after stop of IMP intake was performed. Pregnancy at any time would warrant discontinuation.

3.6.5 Drug concentration assessment

Plasma concentration of (−)-OSU6162 was measured 60-120 minutes after the morning dose (observed intake on site) after 8 weeks of treatment, or 12 weeks after treatment if the 8 week mark was missed. The exact time between last intake of IMP and blood sampling was specified in minutes. One 4 ml Lithium-Heparin tube was used. The tube was filled with blood and centrifuged for 10 min, at 3000-4000 rpm in room temperature. At least 0,25 ml of plasma from the tube is pipetted into a cryo tube. The tube is marked with ACPK-test, patient code, date, time of day and visit number. The sample was immediately frozen in -80°C and stored in our biobank. Upon completion of the study and unblinding of data, samples from patients that received (−)-OSU6162 was sent for analysis of (−)-OSU6162 blood concentration to an external laboratory.

3.7 Data analysis and statistics

Data analyses were performed using the statistical package SPSS for Windows, version 25.0 for papers I-II and version 26.0 for paper III (SPSS, Inc., Chicago, Illinois). A p-value below 0.05 was considered statistically significant in all analyses if not otherwise specified.

3.7.1 Determination of sample size

Sample size calculations were based on the variability in the FSS scores obtained from the available literature on aSAH (12, 132, 277). In the RCT study, with a two-sided 5% level of significance and 95% power, we estimated the sample size of two independent groups to be 34 patients to detect a group difference of 1.5 point (ie. 21,4% change of mean FSS score). We also added an estimated drop out rate of 15%. We therefore concluded a need of 40 patients in each group, a total sample size of 80 patients.

3.7.2 Statistical analyses in paper I-III

In **paper I**, descriptive statistics with mean and standard deviation (SD) or proportions (percentages) were reported for patient characteristics. Differences in continuous variables between groups were tested using independent sample *t* test or one-way ANOVA, whereas differences between categorical variables were tested using the Chi-Square test. The Mantel-Haenszel test was applied to evaluate the frequency of fatigue across time intervals in years since ictus. Univariable logistic regression analyses were performed to identify predictors of fatigue after aSAH. Further, any variable with $p < 0.05$ was implemented in the subsequent multivariable logistic regression analyses with manual backward elimination. The associations between predictors and fatigue were quantified by odds ratio (OR) with 95% confidence interval (CI). The first author, together with co-author Angelika Sorteberg and co-author and statistician Cathrine Brunborg, performed the statistical analyses.

In **paper II**, descriptive statistics were presented with mean and standard deviation (SD) or proportions (percentages) for patient characteristics with the exception of age that was presented with median and range. Continuous variables were presented by mean and SD, and differences between groups were tested using independent sample *t*-test. Continuous variables which were not normally distributed were presented with median and range, and the Mann-Whitney *U* test was used to test for differences between groups. Categorical variables were presented as frequencies or percentages, and differences between groups were tested using the Chi-Square test. An itemized analysis was conducted to explore prominent features of post-aSAH fatigue, by comparing the mean FSS and mean MFS item scores against the mean FSS score ± 2 SEM and mean MFS item score ± 2 SEM for the whole group. The results of the itemized analysis was compared to the results of skewness (i.e., highest negative values) for correspondence. Further, bivariate and partial Pearson correlation coefficient was employed to explore FSS and MFS scores with continuous variables and adjust for covariates. The first author, together with co-author Angelika Sorteberg and co-author and statistician Cathrine Brunborg, performed the statistical analyses.

In **paper III**, descriptive statistics of continuous data were presented as mean and SD if normally distributed, and median with interquartile range (IQR) if not normally distributed. Categorical data were presented as percentages and differences between groups were analyzed with Chi-Square test. Differences in primary and secondary outcome measures from baseline

to each point of assessment were analyzed with paired sample *t*-test or Wilcoxon rank-sum test as appropriate. For comparison of effect between treatment groups, independent samples *t*-test or the Mann-Whitney *U* test was used, depending on the distribution of observed differences. Analyses were conducted according to the intention-to-treat principle and criteria for full analysis set defined in the statistical analyses plan, leaving all 96 patients randomized to treatment included in analyses. The last author performed the statistical analyses.

3.8 Research ethics

Data in the present study were acquired within the RCT "(−)-OSU6162 in the treatment of fatigue and other neuropsychological sequelae after aneurysmal subarachnoid hemorrhage – a double-blind, randomized, placebo-controlled study", approved by the Regional Ethics Committee (REC, 2016/2214) and the Norwegian Medicines Agency, and performed in accordance with the study protocol. The RCT was registered in ClinicalTrials.gov (NCT number: NCT03209830) and EU Clinical Trials Register (EudraCT number: 2016-004739-19) and performed in accordance with good clinical practice (GCP) guidelines and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

4 Summary of papers

4.1 Participants

A total of 726 patients were admitted for non-traumatic aSAH between January 2012 and December 2017, of which 71 died without active treatment (deemed unsalvageable). Of the 655 patients who received active treatment, 238 (36.3%) patients were not eligible for telephone interview mainly due to death (*n*=138) or being severely disabled/resided in a nursing home (*n*=69). The remaining 417 patients were contacted, but 30 (7.2%) did not respond or were impossible to trace, 21 (5.0%) had insufficient skills in Norwegian to understand and/or answer the questions and 10 (2.4%) declined participation. The remaining 356 patients completed the telephone interview ('prescreening') and were included in paper I.

Participants in paper I consisted of 115 (32.3%) men and 241 (67.7%) women with a mean age of 55.7 (±12.5) years at ictus. The average time from aSAH to assessment was 3 years (37.6 months) with a range from 12 to 81 months. Participants from the entire range of hemorrhage severity and neurological dysfunction at admission were included, but most participants were classified as HH 1-3 and GCS 15-14 (79.8% and 66.3%, respectively). A majority of the participants (84.9%) had an aneurysm located in the anterior circulation (43.3% MCA/ICA and 41.6% ACoA/ACA). Two (0.6%) participants had spontaneous aneurysm thrombosis, while the rest were treated with traditional modes of aneurysm repair (54.5% with endovascular treatment and 42.7% with craniotomy and clipping).

In paper II and III, 23 patients treated for aSAH between January 2018 and March 2018 were also added. One of the 23 patients died before aneurysm repair. Of the 22 patients who received active treatment, nine were not eligible for telephone interview. The reasons were death (n=6) or severe disability (n=3). Of the 13 patients that were contacted, one patient declined to participate. The remaining 12 patients completed the telephone interview ('prescreening') and were added to the recruitment flow as described for paper I. Thus, when combining the results for patients treated for aSAH between January 2012 and March 2018, a total of 749 were treated for aSAH, 677 received active treatment, 430 were eligible for telephone interview and 368 patients completed the prescreening by telephone (see Figure 6).

Further, a total of 268 (72.8%) patients were excluded for paper II-III after the telephone interview. The reasons were absence of fatigue as defined by FSS mean score <4 at prescreening (36.4%), decline further participation (19.3%), fulfillment of one or more of the exclusion criteria (16.8%), or death (0.3%). As a result, 100 patients visited the DPMR at OUH for screening and consent for participation in the RCT.

Of the 100 patients that were included in the RCT study, one withdrew and three were excluded (one patient with no clinical signs of fatigue and/or FSS mean score <4, in one patient untreated hydrocephalus was suspected and thereafter confirmed by MRI and measurement of ICP, and one patient had signs of kidney failure demonstrated by blood sample). Hence, 96 patients were randomized for treatment. Even though a total of five patients were either excluded or withdrew from the study during active treatment, all 96 randomized patients were included in the primary efficacy analysis because they took at least one dose of IMP and had at least one post-baseline assessment of the primary efficacy variable which was the criteria for full analysis set.

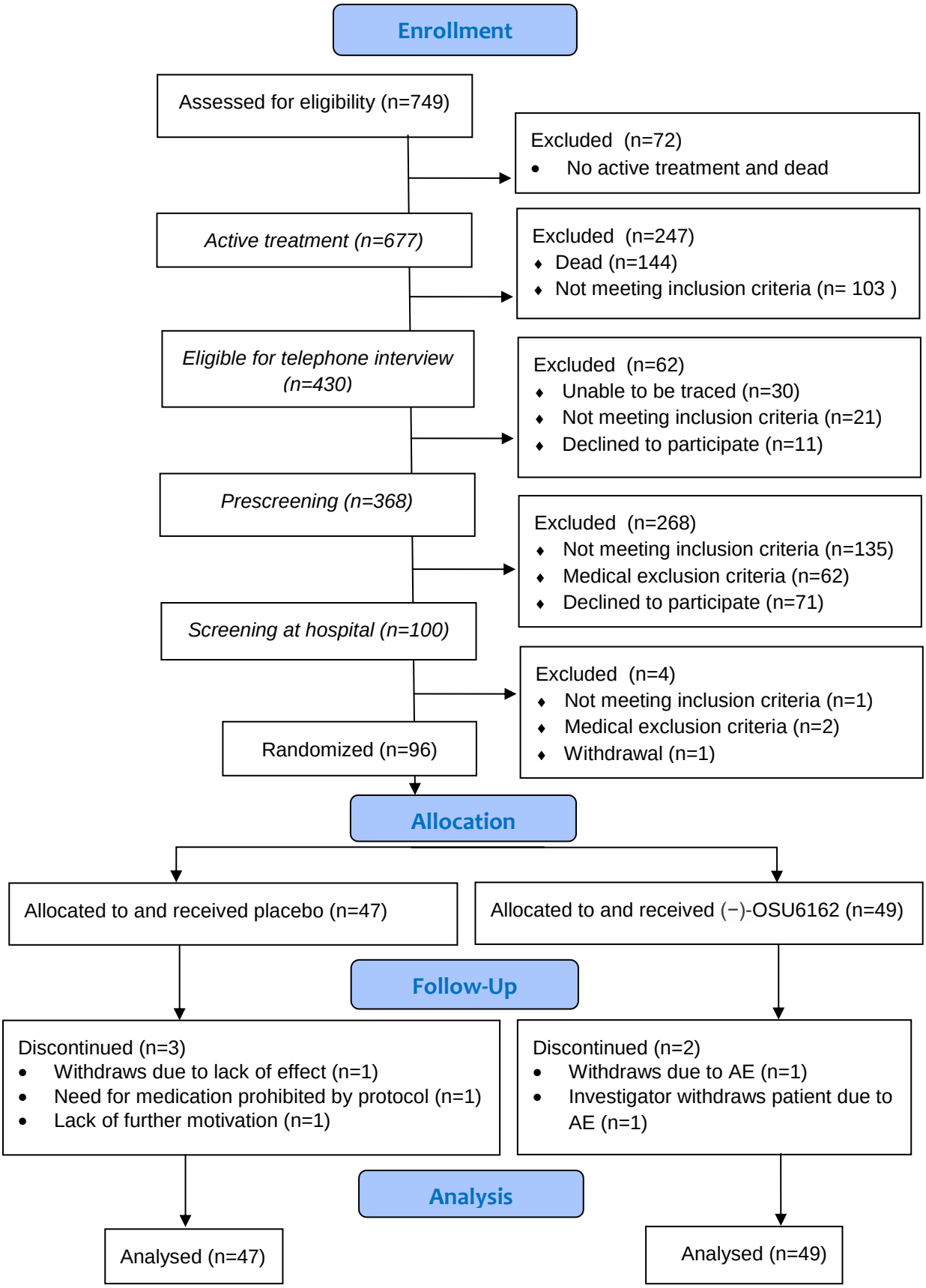

Figure 6. Patient enrollment for the RCT along with randomization to treatment (paper II-III).

The 96 participants included in paper II consisted of 31 (32.3%) men and 65 (67.7%) women with a median age of 57 (22-74) years at assessment. The median time from hemorrhage to assessment was 25 (12-83) months. Participants from the entire range of hemorrhage severity were included, but a majority (72.9%) was classified as good grade according to score on Hunt and Hess scale at admission (HH 1-3 versus HH 4-5). Most of the participants had an aneurysm affecting anterior circulation (86.5%) in contrast to posterior circulation (13.5%). Mode of aneurysm repair was surgical clipping (44.8%) and endovascular treatment (55.2%). No significant difference existed between the 96 study participants and the 272 excluded patients with respect to gender ($p = 0.886$), aneurysm localization ($p = 0.540$) or mode of aneurysm repair ($p = 0.969$). However, the excluded patients were significantly older at the time of hemorrhage ($p = <0.001$) and in better clinical condition prior to aneurysm repair (HH 1-3 versus HH 4-5, $p = 0.038$) as compared to the included patients.

Further, participants were randomized to treatment with (−)-OSU6162 (n=49) or placebo (n=47). There were no significant differences between treatment groups regarding baseline demographic and clinical characteristics except from a higher frequency of frontal cerebral infarction ($p = 0.046$) and more neurological problems mainly attributed to chronic headaches ($p = 0.025$) in the (−)-OSU6162 group compared to the placebo group. Nevertheless, none of the included patients had significant neurological deficits (all categorized as “good outcome” by mRS score 0-2). Regarding medication dosage (up to 60 mg/day) during treatment, no significant differences occurred between the (−)-OSU6162 and the placebo group at week 4 and 8 ($p = 0.710$; $p = 0.345$, respectively). However, dose reduction and study withdrawal due to side effects occurred more often in the (−)-OSU6162 group (16.3% and 4.1%, respectively) than the placebo group (6.4% and 0.0%, respectively, $p = 0.045$).

4.2 Paper I

- Is fatigue a frequent and long-lasting symptom after aSAH?

We found fatigue to be present in 69.7%. The mean FSS score for all the participants was 4.7 (SD, 1.7). The frequency of fatigue was shown to be stable over a time span from 1 and up to 7 years after the ictus ($p = 0.057$). We therefore concluded that fatigue is highly frequent and best considered a chronic condition beyond one year after aSAH.

- Are factors in regards to management and complications of aSAH predictive for the development of fatigue after aSAH?

A univariable logistic regression analyses demonstrated several aSAH-related characteristics to be statistically significant predictors for the development of fatigue in the chronic phase: Nicotine use ($p < 0.001$), reduced consciousness at admission (GCS 13-9, $p = 0.013$; GCS 8–3, $p = 0.017$), larger amount of subarachnoid blood (modified Fisher scales 3 and 4, $p = 0.008$), LOCi ($p = 0.004$), rebleeding before aneurysm repair ($p = 0.043$), severe vasospasm ($p = 0.013$), and acute hydrocephalus ($p = 0.002$).

- If so, are the significant predictors indicative of higher severity of hemorrhage and consequently more complications?

A multivariable logistic regression analyses with manual backward elimination identified three independent predictors for post-aSAH fatigue: Reduced consciousness at admission (GCS 13–9, $p = 0.014$; GCS 8–3, $p = 0.040$) indicative of higher severity of hemorrhage and severe vasospasm during management of aSAH ($p = 0.028$) indicative of complications during management of aSAH. These variables were independent of each other and represented predictors that approximately doubled the odds for the development of post-aSAH fatigue (OR 2.49, 2.13, and 2.30, respectively). However, a history of nicotine use as a premorbid lifestyle factor was the strongest independent predictor ($p = 0.002$) of them all.

4.3 Paper II

- What are the prominent features of fatigue after aSAH?

The results of the itemized analyses for FSS and MFS showed certain fatigue features to be prominent (see Figure 7 and 8 respectively). On the FSS, motivational problems (item 1: 6.5 ± 1.0) and fatigue being one of the most disabling symptoms (item 8: 6.6 ± 0.7) were rated with highest scores. Fatigue due to physical activity (item 2: 4.7 ± 2.0) was scored the lowest. On the MFS, mental fatigue (item 3: 1.9 ± 0.5) and sensitivity to stress (item 8: 1.9 ± 0.9) stood out with the highest scores whereas decreased sleep (item 13: 0.2 ± 0.8) was scored the lowest. FSS and MFS items scores for the entire group were also compared to the item scores for the subgroup of patients with mood disorders.

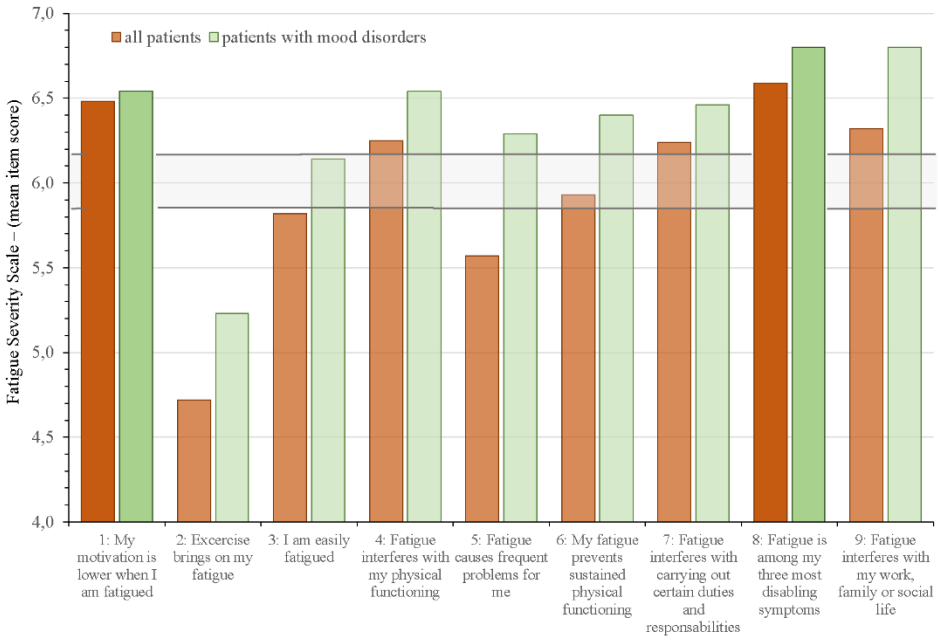

Figure 7. Mean FSS item scores for entire group and allocation into subgroup of patients with mood disorders against the mean FSS score ± 2 SEM (horizontal lines). The two FSS items with the highest mean scores are highlighted. Adapted from paper II.

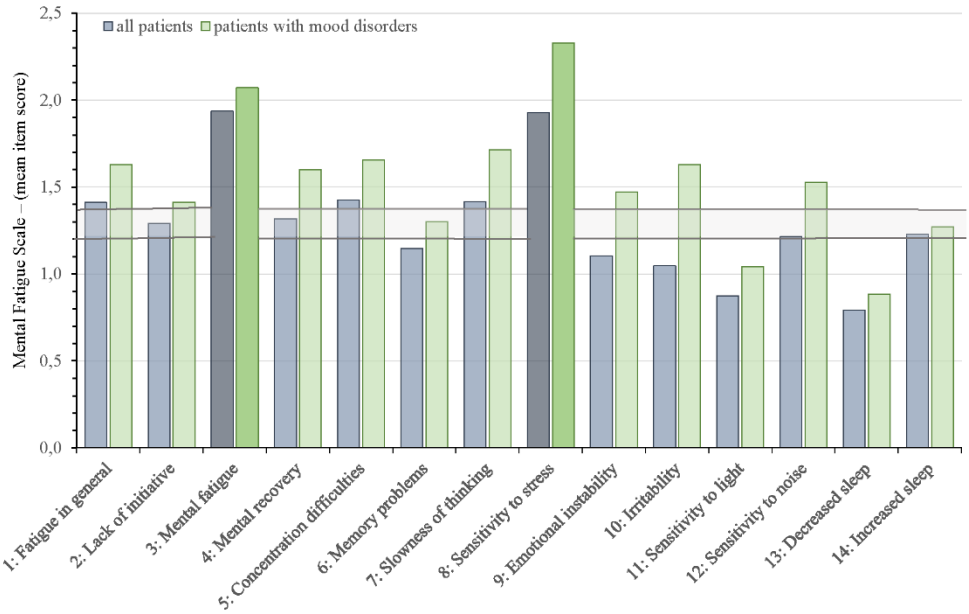

Figure 8. Mean MFS item scores for entire group and allocation into subgroup of patients with mood disorders against the mean MFS score ± 2 SEM (horizontal lines). The two MFS items with the highest mean scores are highlighted. Adapted from paper II.

Further, fatigue was not found to correlate with neurological impairment as scored with NIHSS (FSS: $p = 0.583$; MFS: $p = 0.094$) nor clinical outcome as scored with mRS (FSS: $p = 0.578$; MFS: $p = 0.093$). Weight gain was significantly associated only with mean FSS scores (FSS: $p = 0.016$; MFS: $p = 0.128$), but not when adjusted for depressive symptoms (BDI-II) ($p = 0.140$). Overall, this study strengthens the notion that post-aSAH fatigue has the characteristics of a mental form of fatigue and to a less extent a physical form of fatigue.

- Is fatigue after aSAH distinct from emotional problems, such as depression and anxiety?

Clinical depression (BDI-II score ≥20) and clinical anxiety (BAI score ≥16) was present in 34.4% and 18.8%, respectively. There was a positive correlation between depressive symptoms (BDI-II) and scores on both fatigue PROMS (FSS, $p = <0.001$; MFS, $p = <0.001$), even when adjusted for anxiety symptoms (BAI) ($p = <0.001$; $p = 0.003$, respectively). The relationship between anxiety symptoms (BAI) and scores on fatigue PROMS was mixed, either no longer significant or weakened when adjusted for depressive symptoms (BDI-II) (FSS: $p = 0.833$; MFS: $p = 0.043$). Patients with prior history of depression had higher scores of depressive symptoms (BDI-II) and anxiety symptoms (BAI) compared to those without a prior history of depression ($p = 0.002$; $p = \leq 0.001$). In contrast, patients with prior history of anxiety only had higher anxiety symptoms (BAI) ($p = 0.003$), but not higher depressive symptoms (BDI-II) ($p = 0.209$), compared to those with no prior history of anxiety. Demographical data and aSAH-related characteristics were not significantly related to symptoms of depression (BDI-II) nor anxiety (BAI). However, there was a trend towards higher depressive symptoms (BDI-II) ($p = 0.058$) seen in relation to significantly higher frequency of mood disorders among patients with endovascular as opposed to surgical aneurysm repair (47.2% vs. 23.3%, $p = 0.019$). Taken together, these findings suggest that post-aSAH fatigue and mood disorders, especially depression, are related, but should be considered as distinct constructs since the overlap was incomplete (65.6% and 81.2% did not have clinical depression or anxiety, respectively).

- Is fatigue after aSAH a subjective experience not related to objective performance fatigability as measured with neuropsychological tests?

The neuropsychological test performances indicated a relatively low frequency of cognitive deficits (3.9-8.7%) within the following six cognitive domains: sensomotor function, attention, psychomotor speed, verbal learning, verbal memory and executive function. Digit

Span Forward (WAIS-IV) and CVLT-II recognition hits were negatively correlated with FSS scores (p = 0.040) and MFS sum scores (p = 0.030), respectively, even when adjusted for mood disorders (FSS, p = 0.013; MFS, p = 0.011). Grooved Pegboard dominant hand was negatively correlated with MFS sum scores (p = 0.046), but not when adjusted for mood disorders (p = 0.062). However, fatigue scores were unrelated to the 24 neuropsychological test performance scores since the aforementioned correlations did not remain statistically significant after Bonferroni correction. These findings add to the growing literature of fatigue being a subjective experience most likely not related to objective performance decrement.

- Is fatigue after aSAH related to HRQoL and ability to return to work?

Scores on SF-36 indicated a high frequency of reduced HRQoL (19.8-50.0%). Approximately half of the patients experience reduced HRQoL in the clinical range on the subscales role-physical, vitality and social functioning. All SF-36 were negatively correlated with fatigue PROMS (both mean FSS and MFS sum scores), hence a higher degree of fatigue was associated with poorer HRQoL. Fatigue PROMs were still negatively correlated with all SF-36 subscales when adjusted for mood disorders (p = <.0.05), except for the association between MFS sum scores and General health subscale (p = 0.483).

Of the 78 patients that were employed at the time of hemorrhage, approximately one out of ten (10.3%) had returned to the same amount of work (full RTW), one-third (34.6%) had returned to work with a reduced workload (partial RTW), and half (55.1%) had not returned to work at all (no RTW). A significant difference were found between the mean FSS score and the different RTW categories (p = 0.019). The mean FSS was significantly lower in patients with full RTW as compared to no RTW (p = 0.005), but not when compared to partial RTW (p = 0.085). No difference were found between the MFS sum score and the different RTW categories (p = 0.231). Further, no significant relationship was found between RTW and depressive symptoms (BDI-II, p = 0.199), nor anxiety symptoms (BAI, p = 0.060). Taken together, the results suggest that post-aSAH is strongly related to perceived quality of life and has a role in the ability to return to work.

4.4 Paper III

- Is (−)-OSU6162 superior to placebo in the treatment of fatigue after aSAH?

Primary efficacy was evaluated with the FSS. The mean FSS score improved (decreased) significantly from baseline to every point of assessment (week 1, 4, 8, and 12) for both treatment groups, but remained well below a decrease of 1.5 points (considered clinically significant). There were no statistical difference in FSS points from baseline to the various times of assessment between treatment groups (Figure 9A, upper panel). At the end of treatment (week 12), 21.3% in the (−)-OSU6162 group and 20.5% in the placebo group no longer scored for clinical fatigue (mean FSS score <4, $p = 0.923$).

Subgroup analysis of concomitant medication within the Anatomical Therapeutic Chemical classification system showed improved efficacy of (−)-OSU6162 compared to placebo in patients that used antidepressant during different point of assessment (week 1: $p = 0.047$; week 12: $p = 0.049$; follow-up: $p = 0.049$; Fig. 9A, middle panel). The efficacy of (−)-OSU6162 was also higher in the subgroup with concomitant use of beta- or calcium-channel blockers compared to the placebo group during treatment, but did not reach statistical significance (Fig. 9A, lower panel).

Subgroup analysis of RTW showed a positive treatment effect of (−)-OSU6162 compared to placebo in those with complete RTW on the mean FSS score at week 4, 8 and 12 of treatment ($p = 0.049$, $p = 0.005$, $p = 0.005$, respectively). The main finding of this study therefore suggests that (−)-OSU6162 is not superior to placebo in alleviating post-aSAH fatigue overall, but a potential treatment of fatigue in subgroups of patients with concomitant use of antidepressant and those who had returned to their previous workload.

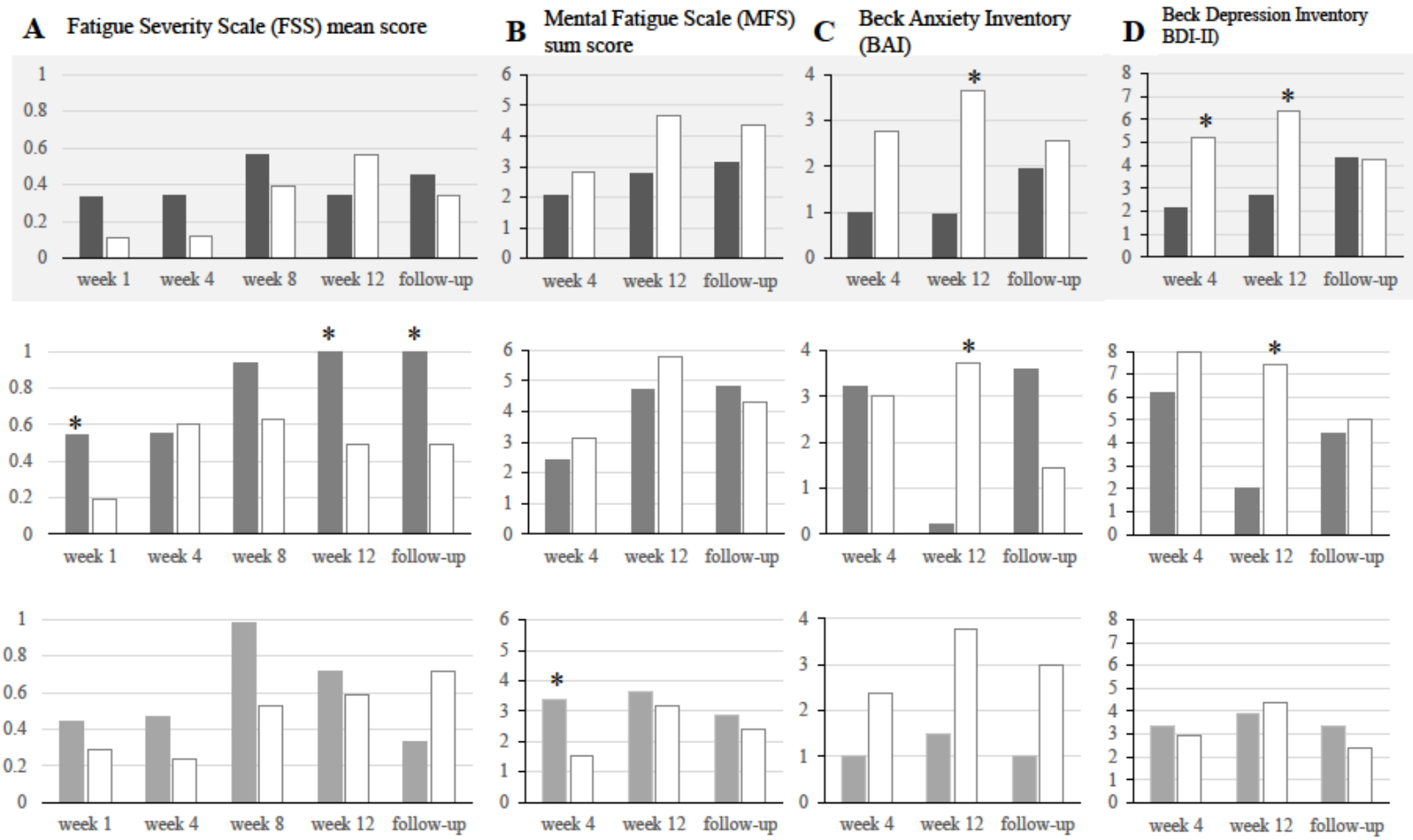

Figure 9. Difference in points from baseline to the different point of assessment for the mean FSS score (A), MFS sum score (B), BAI score (C), and BDI-II score (D) for all patients (upper panel) within treatment arms of (−)-OSU6162 (dark columns) and placebo (white columns). The subsequent panels show results from subgroup analysis of patients with concomitant use of antidepressants (middle panel) and beta- or calcium-channel blocking agents (lower panel). Significant difference between treatment groups * p <0.05. Adapted from paper III.

- Is (−)-OSU6162 superior to placebo in the treatment of other sequelae after aSAH?

Secondary efficacy were evaluated with PROMs (MFS, BAI, BDI-II, and SF-36) and neuropsychological test performances. The MFS sum score improved (decreased) significantly from baseline to week 4 and 12 of treatment, including at follow-up, for both treatment groups. There were no statistical difference in MFS points from baseline to the various times of assessment between treatment groups (Fig. 9B, upper panel). At the end of treatment (week 12), 19.1% in the (−)-OSU6162 group and 25.0% in the placebo group no longer scored for clinical mental fatigue (MFS sum score <10.5, $p = 0.501$). Subgroup analysis showed improved efficacy of (−)-OSU6162 compared to placebo in patients that used beta- or calcium-channel blockers at week 4 (Fig. 9B, lower panel), but this was not found for concomitant use of antidepressants (Fig. 9B, middle panel). Further, no significant group difference was found for MFS in relation to RTW.

Improvement in anxiety symptoms (BAI) at week 12 of treatment and depressive symptoms (BDI-II) at week 4 and 12 of treatment were greater for the placebo group than the (−)-OSU6162 group (Fig. 9C and D, upper panel). The combined use of (−)-OSU6162 and antidepressants was not superior to placebo at week 4 and clearly inferior to placebo at week 12 (Fig. 9 C and D, middle panel). Further, no significant treatment difference between groups was found in the subgroup of patients on concomitant use of beta- or calcium-channel blockers (Fig. 9C and D, lower panel).

HRQoL (SF-36) scores improved significantly from baseline to week 12 of treatment in six (out of eight) domains in the placebo group, as compared to two domains in the (−)-OSU6162 group. The highest degree of improvement was found in the domain Vitality for both groups. No significant treatment difference between groups, or subgroups of concomitant medication, were found in any of the eight domains of SF-36 (see Supplementary Fig. 1, section 8.5).

Regarding the neuropsychological test performances (24 sub scores within six different cognitive domains), no significant treatment difference between groups were found within domains after 12 weeks of treatment (see Supplementary Table 1, section 8.5). Nevertheless, the placebo group improved more in one subtest of psychomotor speed (CWIT 1, D-KEFS) and the (−)-OSU6162 group improved more in one subtest of executive function (CWIT 4, D-KEFS) after 12 weeks of treatment. However, scores for both these subtests were well within the normal range at baseline and a clinically relevant change was debatable (roughly

estimated as a change from 48th percentile to 50th percentile, and 46.5th percentile to 53.5th percentile, respectively).

Therefore, the second major findings in this study was (−)-OSU6162 not being superior to placebo in alleviating mental fatigue (as measured with MFS) after aSAH, but possibly a potential treatment in subgroups of patients with concomitant use of beta- or calcium-channel blockers. Further, the placebo response was stronger than the effect of (−)-OSU6162 on anxiety symptoms (BAI) and depressive symptoms (BDI-II), and we found no significant treatment difference between groups on HRQoL (SF-36) and neuropsychological test performance.

- Is plasma concentration of (−)-OSU6162 associated with clinical improvement?

Plasma concentration of (−)-OSU6162 (based on blood test at a mean of 74 minutes after drug intake) at week 8 of treatment varied between 0.125 and 0.870 µM, and was not related to BMI (p = 0.938) or weight (p = 0.497). When stratified according to dosage (30 mg or 60 mg/day), there was a significant correlation between improvement in FSS mean score and higher plasma concentration in those that had taken 60 mg/day (p = 0.002). The same trend was seen for MFS sum score, but did not reach statistical significance (p = 0.085). The decrease in anxiety and depressive symptoms was also significantly correlated to plasma concentration in those that had taken 60 mg/day (BAI: p = 0.020; BDI-II: p = 0.025). Further, no significant association was found between fatigue PROMs and plasma concentration in those that had taken 30 mg/day (FSS: p = 0.920; MFS: p = 0.649). Results regarding plasma concentration of (−)-OSU6162 can be interpreted as evidence of mechanistically separate effects of (−)-OSU6162 and placebo, or to a certain degree in favor of a pharmacological effect of (−)-OSU6162.

No serious AEs were attributable to the treatment, but dizziness was more common in the (−)-OSU6162 group compared to the placebo group (24.5% vs 6.4%, p = 0.015). Hence, (−)-OSU6162 was found to be safe and well tolerated.

5 Discussion

The present thesis reports on a cross-sectional study (paper I), baseline assessment (paper II) and treatment outcome of a RCT (paper III) in survivors after aSAH. The discussion is divided into sections where the major findings of the three papers are discussed subsequently. Thus, methodological issues of the present studies and within the field are discussed throughout where general methodological considerations are presented in the last section.

5.1 Post-aSAH fatigue is a frequent and long-lasting symptom

In line with earlier studies, we found post-aSAH fatigue to be a frequent (69.7%) symptom in the chronic phase (≥1 year) after hemorrhage. In the absence of a specific fatigue PROM validated in the aSAH population, we chose the widely used FSS with evidence of high internal consistency (189). When assessing post-aSAH fatigue by means of the FSS (mean FSS score ≥4) at least one year after ictus, previous frequency estimates have been between 60% and 71% (126-128, 131, 132). Studies using other instruments than FSS report that fatigue was present in approximately half of the aSAH population. Studies that merely used single questions to assess fatigue reported highly variable prevalence from 31% up to 90% (118-122). The exact estimate of fatigue frequency clearly depends on the chosen tool of assessment, but there are strong indications that post-aSAH fatigue is a highly frequent symptom in the chronic phase. The contribution of our study has been to confirm earlier studies demonstrating a high prevalence of post-aSAH fatigue, but with a sample size more than three times larger than in earlies studies rendering our results more robust.

Variation of fatigue prevalence among studies may not solely be related to the chosen PROMs, but can also be related to timing of assessment. We found post-aSAH fatigue to be a relatively stable and long lasting symptom beyond one year after hemorrhage, although a cross-sectional design has inherent limitations regarding firm conclusions of time course. This result is similar to the consistency in fatigue levels found in previous longitudinal studies with baseline assessment at 5-9 months and follow-up assessment beyond one year after ictus (119, 120, 131, 132). In contrast, longitudinal studies that assessed fatigue within one year after hemorrhage (3 months versus 9-10 months) found a decrease in fatigue levels (124, 125).

Kutlubaev and colleagues (12) have postulated that there might be different mechanisms involved for the development of fatigue according to time elapsed since ictus. Somewhat comparable to our findings, a recent cross-sectional study by Samuelsson et al. (113) found moderate/severe fatigue to be present in about one third (25.0-38.8%) of aSAH survivors up to 21 years after hemorrhage. Also, in a meta-analysis by Cumming et al. (114), it was concluded that post-stroke fatigue was persistent across time and not accounted for by timing of assessment despite a marked between-study variability in the estimate of fatigue prevalence. Together with previous studies of post-aSAH fatigue prevalence, our results suggest that post-aSAH fatigue beyond one year should be considered as a chronic condition.

Our results also confirms previous findings (113) of a high frequency or severe fatigue even in aSAH patients graded as being in good neurological condition (mRS score 0-2). It is further noted that there are strong indications of post-aSAH fatigue exceeding the prevalence of post-stroke fatigue where the latter was estimated to be approximately 50% (114, 115), supporting the preliminary evidence that fatigue after hemorrhagic stroke is more frequent than after ischemic stroke (115).

5.2 Predictors of post-aSAH fatigue

In the last two decades, only a handful of studies have investigated the relationship between post-aSAH fatigue and the cascade of deleterious events as a result of the hemorrhage. A relatively low sample size and limitations regarding statistical power have been a challenge when investigating predictors for the development of post-aSAH fatigue. Previous samples have yielded <80 patients with post-aSAH fatigue (124, 128, 132), where the number of patients with post-aSAH fatigue is unknown in the study by Buunk et al. (133) since results were reported collectively for patients with both aneurysmal and angiographically negative SAH. In comparison, we performed our statistical analyses in a study population of 248 and 108 aSAH patients with and without fatigue, respectively. Since there is limited knowledge on the relationship between aSAH-related factors and fatigue, our exploration had the intention to aim broadly.

Similarly to our results, previous studies have also failed to find an association between post-aSAH fatigue, age (124, 128, 132), sex (124, 128, 132), aneurysm repair method (128, 133)

and localization of aneurysm/aneurysm circulation (128, 133). However, the results of our univariable regression analysis demonstrated a range of other aSAH-related factors to be significant predictors of post-aSAH fatigue in the chronic phase. Since there is overwhelming evidence of interdependence between the aSAH-related factors, a multivariable regression analysis with manual backward elimination was also performed. The results of this analysis was that nicotine use, reduced consciousness at admission (GCS <14) and severe vasospasm were independent predictors which approximately doubled the odds for the development of post-aSAH fatigue.

Overall, the results from previous studies regarding potential predictors have been mixed. First, the results regarding GCS <14 as an independent predictor is similar to that found in Khajeh et al. (132), where severity of aSAH (WFNS score >1) was associated with fatigue. However, this was not found in the study by Rödholm et al. (124) nor in the study by Buunk et al. (133). LOCi and GCS (reflects degree of conscious state) are relatable constructs and assumed to be highly interdependent, which can explain the findings of LOCi only being statistically significant after univariable regression analyses whereas GCS <14 was an significant predictor also after multivariable regression analysis. Prolonged LOCi is reflected in cerebral circulatory arrest of varying length (decreased CPP) and will therefore result in the patient being admitted with a reduced GCS score. There is evidence that even transient decreases in CPP can lead to cerebral ischemia and contribute to early brain injury, hence contribute in the development of post-aSAH fatigue.

It has been stated that the mechanisms of early brain injury in relation to LOCi might be pathophysiologically distinct from late or delayed brain injury due to vasospasm (49, 278), which is noteworthy in the light of finding GCS <14 (reduced consciousness) and severe vasospasm as separate and unique contributors in the development of post-aSAH fatigue. Reduced consciousness at admission and vasospasms may therefore represent distinct mechanisms in different phases of pathophysiological events leading to brain injury after aSAH, and ultimately to the development of post-aSAH fatigue. In contrast to our findings, Khajeh et al. (132) did not find a significant relationship between fatigue and vasospasm. The number of patients with vasospasm are not given in the previous study, and one can assume that the subpopulation of patients with vasospasm were small since the cohort consisted of 84 aSAH patients in total. Further, different definitions of vasospasm impede direct comparison of studies. In our study vasospasm referred to angiographical or sonographic vessel narrowing of varying degree and not to DCI.

A part from sample size and high degree of intercorrelation between the aSAH-related factors, differences in how these variables were evaluated may partially explain the discrepancy in results. Many of the aSAH-related variables are semi-continuous and the problems associated with dichotomization is loss of statistical power and oversimplification of the relation between the predictor variables and outcome (279). Dichotomization requires the choice of a cut point, which in itself is problematic. An option to this issue can be to select a clinically meaningful criterion based on current clinical practice or scientific knowledge, where we primarily chose the former option. However, caution is warranted when making comparisons between studies with different categorization of variables, also when it comes to validity of the analysis and generalizability of the results.

Finally, yet importantly, nicotine use leading up to the hemorrhage was the strongest independent predictor in the multivariable regression model. Nicotine dependency involves the mesocorticolimbic dopamine system and influence rewards, addiction and withdrawl – the same dopaminergic pathway postulated to be involved in the development of fatigue (136, 137, 181). A chronic use of nicotine can therefore lead to changes in dopamine function. (280). Pro-inflammatory factors (such as IL-8, IL-1β, TNF-α) are possibly involved in the inflammatory response triggered by tobacco smoking, and nicotine can aggravate ischemic brain injury (281). Even though there are indirect and limited evidence of a link between nicotine and fatigue in aSAH survivors, nicotine use should be explored as a potential factor related to post-aSAH fatigue in future studies. Further, this study strengthens the current empirical evidence of nicotine use as a unique risk factor in the interdependent and complex relationship going from aneurysm formation and rupture, complications during management and neuropsychological outcome in the chronic phase. No other studies have investigated the relationship between nicotine use and post-aSAH fatigue, and we have therefore extended our knowledge of the role of nicotine use beyond neurological outcome.

Taken together, our study found independent risk factors across different phases of aSAH: from a modifiable life style factor leading up to the IA rupture (nicotine use), to clinical presentation at admission (GCS <14) and the presence of complication during management of aSAH (severe vasospasm). The results reported here appear to support an assumption of a cascade of pathophysiological events after aSAH consequently leading to post-aSAH fatigue, although a great deal of caution should be taken when interpreting the results from this type of study design regarding pathophysiology.

Furthermore, the present results cannot necessarily be extrapolated to all aSAH patients with fatigue. Even though we included patients from the entire range of aSAH severity, we excluded patients with pronounced sequelae (i.e., aphasia, severe cognitive impairment) unable to conduct the study procedures in a valid manner. Nevertheless, we hypothesized based on evidence from this study in combination with the growing literature on the role of inflammation in fatigue (182) that pro-inflammatory cytokines causing dopamine imbalance may be a common denominator for the presently identified predictors in the development of post-aSAH fatigue (see Figure 10). Besides the findings from our study, the premises for this postulation was also the growing evidence of a relationship between neuroinflammation and SAH (85, 89, 91-93) and cerebrovascular diseases in general (151-153), in combination with fatigue being a common symptom in diseases related to different aspects of inflammation (autoimmune, autoinflammatory and inflammatory disorders).

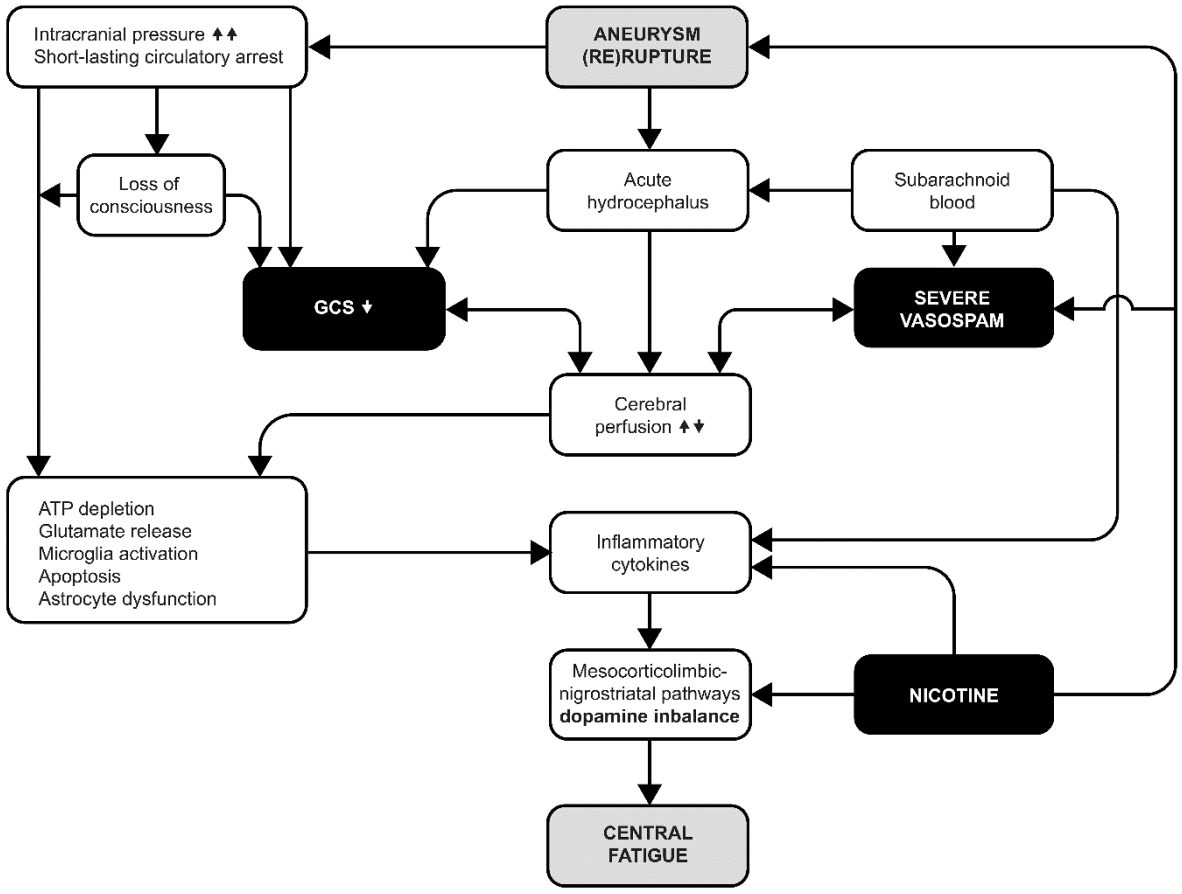

Figure 10. Illustration of the complex and interdependent relationship between aSAH-related variables in the processes attributable to post-aSAH fatigue. Black boxes indicate independent predictors of post-aSAH fatigue in our study. Adapted from paper I.

5.3 Post-aSAH fatigue – clinical presentation

Our results indicate that post-aSAH fatigue are associated with a mental type of fatigue, and to a less extent a physical type. A recent study have also highlighted the presence of this pattern of fatigue after aSAH (133). Our itemized analyses showed highest scores on our fatigue PROMs for "low motivation" (FSS item 1), "fatigue is among my three most disabling symptoms" (FSS item 8), "mental fatigue" (MFS item 3) and "sensitivity to stress" (MFS item 8). The lowest scores were for "fatigue due to exercise" (FSS item 2) and "decreased sleep" (MFS item 13). Further, neither weight gain nor neurological (physical) status was associated with fatigue.

Mental fatigue (MFS item 3), as reflected in the highest score on the MFS, was defined as becoming quickly fatigued and with the need to take a break or do something else more often than before. The examples given for this item was becoming quickly fatigued when thinking hard, performing tasks (reading, watching TV), and taking part in conversation with several people. As one can see by the item description, it is postulated that mental fatigue is closely related to cognitive performance. Induced fatigue in healthy controls has been linked to cognitive performance decrement (282, 283), but the relationship is not always clear cut (284), even so for clinical populations (141, 199). We found no significant correlation between any of the 24 neuropsychological test scores and fatigue PROMs. Hence, our results did not support a relationship between subjective fatigue and performance fatigability.

Further, we found performances on the cognitive tests mainly to be within normal variation on a group level. What is of clinical interest is that none of our participants had to discontinue performance during assessment with the neuropsychological test battery over a time period of 90 minutes, but many unprompted reported that they needed several days of rest due to fatigue *after* the assessment. Although somewhat counter intuitive, this could perhaps be understood as post-aSAH fatigue being reflective of the high mental effort required to perform cognitive tasks over a certain duration irrespective of task complexity (285). That is, patients with fatigue can compensate for cognitive deficits, albeit small according to norms, by increased effort. This is in line with the characterization of mental fatigue after TBI as proposed by Johansson & Rönnbäck (144), where over-exertion leads to a long recovery time disproportionate to the exertion level.

Clinical neuropsychological tests were traditionally developed to identify and assess brain damage (286). These measures have been criticized to be too crude or insensitive (i.e., low ecological validity) to subtle cognitive impairments or predicting real-world functioning, especially for executive function and social cognition (287, 288). That being said, the tests included in our neuropsychological test battery has been demonstrated to be sensitive, valid and utile in previous studies of the aSAH population (289). The fact that aSAH survivors were selected based on the presence of fatigue also had to be taken into account and the assessment kept as short as possible.

In our study, test performances was mainly adjusted for age and gender, but they were not adjusted individually according to estimated premorbid level of cognitive function. Our group of patients were highly educated according to international standards (49.0% had completed undergraduate or graduate school). It has been stated that cross-national differences in IQ scores can be partially related to better educational systems in Europe as compared to the US (290), where normative data is collected from the latter sample in most standardized tests. Further, we found higher degree of fatigue to be correlated with reduced quality of life and partially to inability to return to work. Hence, one can speculate if the cognitive tests we employed were too insensitive to the subtle and higher-order cognitive dysfunction that these patients may experience as a result of the hemorrhage.

Therefore, fatigue might be reflective of high effort (203), where patients can compensate for subtle cognitive impairment through increased effort, but at a certain costs, namely mental fatigue. This is an interpretation that warrants caution since we have limited data to support such a claim, but nevertheless fits well with our clinical observations of aSAH survivors with chronic fatigue being able to uphold cognitive performance for the limited time of assessment, but with a prolonged and disproportionate mental fatigue *after* performance. This can also be interpreted as in alignment with other results in our study, where the participants generally show minimal impairment in standardized cognitive testing, while reporting substantial problems with coping in everyday life and at work. The world outside the hospital is more complex and requires a higher level of sustained cognitive performance, and where compensatory strategies may more often become inefficient. Therefore, our 90 minutes test session may have been too short to tap into the ability of sustained cognitive performance. Even though we did not find a statistical association between fatigue and cognitive performance (i.e., fatigability), in combination with the mixed results of this relationship in

other neurological disorders, it seems like methodological challenges needs to be overcome to explore this important avenue for future research.

Also given the close link between mental fatigue and motivation, as proposed by Chaudhuri and Behan (136), it is of interest that we found motivational problems (FSS item 1) to be a key feature of post-aSAH fatigue. It has been stated that the evaluation of predicted rewards and energy expenditure is central to mental fatigue, where people with mental fatigue will not be motivated to engage in task performance when the energy expenditure is perceived to outweigh potential rewards (138). This process of evaluating rewards against potential costs seems to be associated with the so called ”reward system” of the brain and the function of the dopamine neurotransmitter – as mentioned previously, the same dopaminergic system involved in nicotine dependency.

In regards to motivational problems, the item 2 on MFS “lack of initiative” was evaluated as only somewhat difficult and one can speculate if it is more about the (potential) cost than not perceiving the outcome as rewarding. One might assume that motivation is lower if one experiences a high degree of fatigue, but our results can also be interpreted to align with the observation that our patients with post-aSAH fatigue had the drive and motivation to fulfil obligations and perform tasks (high compliance) *despite* experiencing mental fatigue. Most often it was lack of endurance as a result of fatigue that was problematic, as opposed to the motivation in itself, to a certain extent reflected in the items full description: “my motivation is lower *when* [emphasis added] I am fatigued” (188, pp. 1122). It has been suggested that in healthy subjects, the degree of cognitive demands or limited cognitive resources is what trigger cognitive fatigue, not motivational state (291). However, the data and results available from paper II cannot delineate the actual causality of dysfunction in the balance between motivation and energy expenditure. Also, the component of motivation as a subconstruct of fatigue can be related to or overlap with depression as will be discussed later on.

Besides a mental type of fatigue and motivational problems, sensitivity to stress was also a prominent feature of post-aSAH fatigue. This has also been demonstrated by Johansson et al. (197) in the TBI population. There are mixed results regarding the relationship between stress on the one hand and depression or fatigue after aSAH on the other hand (132, 292, 293). Also, the results from paper II are descriptive and the mechanisms behind the heightened sensitivity to stress reported by our participants are largely unknown. With these limitations in mind, from a theoretical standpoint there seems to be a reciprocal relationship between stress and

fatigue that can be reinforced over time. There is a bidirectional communication between the immune system and CNS, where stress induces alterations in immune function (stress-induced neurogenic inflammation) (294). Conditions of chronic inflammation can generate the basis for stress-induced aggravation of disease, thus psychological stress can contribute to chronification of disease processes as well as exacerbation of symptoms in chronic conditions (295, 296). This will be further discussed in the following section in the context of mood disorders.

5.4 Post-aSAH fatigue and mood disorders are related, but distinct constructs

Clinical depression and clinical anxiety (mood disorder) was present in 34.4% and 18.8%, respectively, of our participants with post-aSAH fatigue. Concurrent with the findings in the systematic review by Tang et al. (11), patients with premorbid mood disorders had higher depressive and anxiety symptomatology than patients without this prior history. Further, we found no relationship between aSAH-related factors and mood disorders. We also found depression (and to a lesser extent anxiety) to be strongly associated with fatigue. Passier et al. found, especially in patients without physical or cognitive impairments, that depression, anxiety and passive coping style at 3 months post ictus play an important role in the presence of fatigue 1 year after hemorrhage (128). It should also be noted that our patients with mood disorders had the highest MFS score on item 11, sensitivity to stress. The role of stress is indirectly evident in the development of mood disorders, such as post-traumatic stress disorder (101, 148, 297).

In a review by Felger & Miller (94), it was postulated that the effect on inflammatory cytokines on basal ganglia dopamine might be especially relevant to both depression and fatigue. Stress-induced changes in the immune system that result in neuroinflammation have been suggested to also be involved in the etiology of depressive disorders (298, 299). The cytokine hypothesis of depression (300) postulate that *depression results from an increased production of pro-inflammatory cytokines, which may be triggered by external or internal stressors* (pp. 289). This hypothesis is based on the multiple inflammatory biomarkers that have been detected in depression: increased plasma levels or production of pro-inflammatory cytokines such as IL-1β, IL-6, TNFα, IFNγ and indicators of lowered plasma tryptophan (a

precursor of serotonin and melatonin). The cytokine hypothesis is also fueled by the high comorbidity of depression with inflammatory disorders, such as MS (301).

The relationship between post-aSAH fatigue and depression can be interpreted in the context of stress. Our post-aSAH fatigue patients stands in a split between sustained major stress (large and long-lived release of stress axes mediators due to a life-threatening hemorrhage) and acute minor stress (i.e., function reduction in daily life and direct consequences of these). In regard of the inverse relationship between fatigue score (FSS) and low/intermediate education level as compared to high education level, this can possibly be partially related to socio-economic status as a stressor. FSS measures impact of fatigue, thus patients with lower education perceived their fatigue to have a higher degree of negative consequences. Also, one factor in relation to fatigue and perceived stress not explicitly explored in our data was the unpredictability of fatigue. For MS patients, Hubbard et al. (302) describes fatigue as a transitory state of limited predictability, that is being both predictable (i.e., after engagement) and unpredictable (i.e., without currently identifiable causal link). Our patients often reported that unpredictability was a main source of internal stress (rumination and self-loathing) when trying to understand and self-manage their fatigue. If one was to accept the premises of neuroinflammation and pro-inflammatory cytokines as underlying mechanisms behind fatigue, depression and stress in different diseases, one might speculate if inflammation is the common denominator behind these different neuropsychological "phenotypes" commonly observed after aSAH.

If fatigue and depressive symptoms have common underlying mechanisms and correlate highly, should they be understood as two sides of the same coin? Not surprisingly, item descriptions of fatigue and depression can overlap. The BDI-II asks respondents to choose among description from "I don't get any more tired than usual" to "I am too tired to do anything" (item 15). We tried to overcome this issue by choosing a conservative cut-off, but a certain overlap can still exist. As fatigue and depressive symptoms was assessed concurrently, one can compare the overlap of incidence. A majority of our patients with post-aSAH fatigue did not fulfill the criteria for clinical depression or anxiety (65.6% and 81.2%, respectively). In a recent review and meta-analysis (115), the prevalence of post-aSAH fatigue was found to be higher in studies that included participants with depression compared to those did not (51% versus 41%), but the evidence of a significant difference between the two was deemed as weak ($p = 0.10$). Stroke studies have found heterogeneity in fatigue prevalence not to be explained by depression (114) and that fatigue may occur in the absence of depression (303-

305). Several treatment studies have shown a differential effect of a specific intervention on fatigue and depression (221, 240, 242, 259). Taken together, this lends support to the more commonly accepted notion of fatigue as a distinct concept separate from emotional problems, even though a partial influence cannot be out ruled. However, it should not be underestimated that our subgroup of post-aSAH patients with mood disorders had higher scores on almost all fatigue items, thus higher symptom burden or intensity regarding fatigue.

5.5 Post-aSAH fatigue is related to HRQoL and contributes to low rates of RTW

From a clinical perspective, there is no surprise that post-aSAH fatigue (a mental form of fatigue exacerbated by stress and closely related to motivation) was perceived as one of the most disabling symptoms after hemorrhage (FSS item 8) since the selected group consented to take part in comprehensive study with a hope for successful relief of their fatigue (ie., paper II is based on the baseline assessment of the RCT). In this group of aSAH survivors, we found fatigue to be closely associated to reduced HRQoL (SF-36), even after adjusting for mood disorders. Despite high functional independence and good neurological function, one out of two participants reported physical limitations and reduced social functioning as the most affected aspects when evaluating their quality of life. Our results confirm previous studies that have shown the same divergent pattern between good physical function and problems in the emotional and social domain assessed with QoL PROMs (126), and further post-aSAH fatigue being related to problems with resumption of social activities (130), and lower social participation (120). Even though it may be obvious and rather intuitive that fatigue is related to perceived quality of life, a scientific establishment of this relationship in a sound study is the sole foundation of giving empirical-based advice to our patients and their families instead of being opinionated without being properly informed. If reduced HRQoL is a cause or consequence of post-aSAH fatigue cannot be answered from the aforementioned studies, including ours, since the results are based on correlation analyses.

In our study, 78 out of our 96 aSAH patients were employed (paid work) at the time of ictus, but where only eight (10.3%) had resumed to the same amount of work after the hemorrhage. Although dependent on the definition of RTW, less than 50% of all aSAH patients actually resume to work (306). We found that return to work (RTW) was associated with fatigue (as measured with FSS), but not with mood disorders. In our sample, there was an obvious

discrepancy of so-called good outcome (i.e., high functional independence and low frequency of cognitive deficits) and a surprisingly low rate of RTW. These results align with previous studies that have demonstrated a low rate of RTW after aSAH (13, 127), and most importantly to a study that showed mental fatigue to be associated with low rate of RTW and being a better predictor of functional outcome compared to physical fatigue and mood disorders (149). Our result of significant association between post-aSAH (FSS) and RTW is also equivalent to the results by de Vries et al. (135), who demonstrated that fatigue severity was independently related to worse long-term participation, adjusted for depression and discharge to inpatient rehabilitation. In the first study that examined the relationship between a core set of cognitive functions and RTW, Buunk et al. (149) found self-reported executive impairment in daily life to be a significant predictor of incomplete long-term RTW after hemorrhage. What is interesting is that these domains of cognitive function has been described as "higher-order functions" and can be interpreted in light of postulated mechanisms behind "mental fatigue" as mentioned earlier.

It is obvious that RTW is a multifaceted construct likely to be related to several factors, therefore our analyses have limitations regarding predictive value. However, fatigue should be carefully considered when planning rehabilitation strategies, as it is clearly one important factor related to long-term RTW. Our estimate of RTW must be interpreted in the light of our selected population only consistent of patients with chronic fatigue, and is not necessarily comparable or can be generalized to aSAH cohorts in general. Also, welfare policies differs between countries, hence terms and opportunities for return to work will vary according to geographical localization of the aSAH population being studied.

In summary, post-aSAH fatigue is multidimensional phenomenon characterized by a mental type of fatigue not likely related to neurological status. Even though we did not find a statistical relationship between fatigue and neuropsychological test performance, we cannot rule out that subtle cognitive impairment, especially "higher-order executive functioning skills" not detected by traditional neuropsychological tests, influences and are influenced by the degree of fatigue experienced. Over-exertion as the result of sustained cognitive demands may result in fatigue disproportionate and irrespective of task complexity. We postulate that the mechanisms related to early brain injury (paper I) resulting in inflammatory responses in the brain can be the common denominator for both fatigue and emotional problems, where different stressors are seen as mediator of the intensity and severity of these sequelae. All in all, fatigue has a major impact on perceived quality of life and is partially related to an

inability to resume work life. Our findings also indicate that post-aSAH fatigue permeates all major aspects of life and is an important factor to consider for early interventions.

This was the first study to explore a substantial range of factors previously known to be associated with aSAH in a population exclusively consisting of aSAH patients with chronic fatigue. In summary, our study has provided a deeper insight into the prominent features of post-aSAH fatigue and how the phenomenon can be understood, and potentially how it can be assessed and treated.

5.6 (-)-OSU6162 is not superior to placebo in the treatment of post-aSAH fatigue

Contrary to our hypothesis, 12 weeks of treatment with (−)-OSU6162 had no significant effect on post-aSAH fatigue compared to placebo. That is, both groups showed significant improvement of fatigue levels (FSS). A similar pattern was found on several of the secondary measures, such as mental fatigue (MFS), depressive symptoms (BDI-II) and "Vitality" (SF-36). Nevertheless, a significant correlation between (−)-OSU6162 concentration and improvement in fatigue (FSS), depressive symptoms (BDI-II) and anxiety symptoms (BAI) were found for patients on dose 60 mg/day. Neuropsychological test performances were not affected by treatment. Subgroup analyses revealed a superior effect of (−)-OSU6162 in patients who had returned to their previous workload and a possible synergetic effects of (−)-OSU6162 and medications interfering with dopaminergic pathways, but represents preliminary evidence that should be explored further.

We did not find (−)-OSU6162 to be superior to placebo in the treatment of post-aSAH fatigue. Our main finding is contrary to what have been demonstrated in three RCT double-blind cross-over studies (259, 260, 264). The CONSORT reporting guidelines (307) have not been extended specifically for RCT cross-over trials, but certain methodological pitfalls should be discussed (308, 309). None of these studies included a washout phase between treatment periods as recommended. Even though (−)-OSU6162 is reported to be rapidly absorbed and with a 3 hour half-life (25), it is not unlikely that treatments with (−)-OSU6162 have the potential to induce temporary structural changes at some level in the brain as indicated for antidepressants (310, 311). It is also recommended that results should be analyzed separately by sequence group. Johansson et al. (259) found no significant effect with

respect to order of treatment. However, Kloberg et al. (260) and Nilsson et al. (264) found that patients starting with placebo seemed to respond better to (−)-OSU6162 treatment than the group starting with (−)-OSU6162. For the study by Kloberg et al. (260), the design also allowed for variation in actual treatment length according to allocation even though the length of gap between assessment points was 4 weeks irrespectively.

Our main finding is also contrary to what have been reported in two open-label single-arm studies (262, 265) where (−)-OSU6162 was considered a promising treatment to mitigate fatigue in ME/CFS and MS. However, in an open-label trial, the impact of knowledge of treatment allocation on post-randomized treatment decisions and answering PROMs is more a subject to bias compared to double-blind trials. Prospective randomized controlled trials with double-blinding is commonly viewed as the "gold standard" in trial methodology (312).

Similar to our study, two previous RCT placebo-controlled double-blind studies (263, 313) found a significant improvement of fatigue after treatment, but no significant between-group differences. These trials had at least double the sample size compared to the aforementioned (−)-OSU6162 studies, but the maximum length of treatment period (i.e., 4 weeks) was comparable to RCT cross-over trials. A methodological consideration is warranted for the length of treatment when the symptom of interest is unstable and may naturally fluctuate within a short period of time regardless of interventions.

Can a significant improvement of fatigue after treatment, but with no differences between treatment groups be interpreted as the placebo effect? Placebo effect refer to the beneficial effects that occur in clinical or laboratory medical contexts after administration of an inert treatment or as part of active treatment, due to mechanisms such as the patient's expectations of treatment efficacy (314). In a broad sense, the placebo effect are improvements of a patient's symptoms that are attributable to their participation in the therapeutic encounter, with its rituals, symbols, and interactions (315). The placebo effect has been called into question (316), but there is compelling evidence that the placebo effect is a genuine psychobiological event attributable to the overall therapeutic context (317).

The significance of belief and expectancy is integral to the placebo effect (318, 319). It is highly likely that our patients had a belief in the efficacy of the treatment they received, since many of our patients requested an extended use of the IMP at the end of treatment before unblinding took place. Other context-based confounds can also take place. The halo effect (320) is the patients response towards another individual based on the subject's impression of

that individuals character. Many of our patients expressed boundless trust in a clinical trial lead by the neurosurgeons that saved their lives. Also, in a study by Kaptchuk et al. (321) it was demonstrated that the additional support from the patient-practitioner relationship enhanced the placebo effect compared to pure placebo treatment. This is highly relevant in our study, where patients in an informal way were allocated to the team physician investigator assumed most suitable for the specific patient or that the patient had met during management of aSAH in the hospital. A strong therapeutic alliance is known to facilitate adherence and mediate change irrespective of psychotherapy modality (322, 323). However, our placebo-controlled RCT do not generate data that permit a true delineation of the apparent placebo effect from the true placebo effect (324), since we did not have a no-treatment/waiting list control group.

What is of especial interest in the context of our RCT trial, is that the same neurobiological mechanisms might be at play for both (−)-OSU6162 and the placebo effect. The placebo effect has been associated with the release of dopamine, at least in patients with PD (325-327). It has further been argued that expectation of therapeutic benefit can been seen as analogous to expectation of rewards (328). Hence, the neurobiological basis of fatigue and the placebo effect have the potential of a certain overlap since motivation, a central component of fatigue (136), is related to expected rewards and benefits. The mechanisms involving the dopamine system may be common for both the placebo effect and (−)-OSU6162, also discusses in detail by Nilsson al. (263).

In favor of a potential pharmacological effect of (−)-OSU6162 is the correlation between higher plasma concentration of (−)-OSU6162 in those that had taken 60 mg/day and improvement in fatigue (FSS), decrease in anxiety symptoms (BAI), and decrease in depressive symptoms (BDI-II). Similar to our findings, Nilsson and colleagues (263) found (−)-OSU6162 concentration to correlate with improvement in mental fatigue (MFS), observer's rating of fatigue (FF) and depressive symptoms (BDI) in ME/CFS patients. Also similar to our findings, they found a larger treatment effect of (−)-OSU6162 on fatigue in ME/CFS patients on antidepressants than those without this concomitant treatment. These results were in contrast to the findings by Berginström and colleagues (313), where (−)-OSU6162 concentration was not associated with outcome after TBI. However, the mean plasma concentration in the latter study was deemed as low (0.01-0.32 µM).

In paper III, we discussed if the findings of enhanced efficacy of (-)-OSU6162 in patients with concomitant use of antidepressants (SSRIs) or beta- or calcium-channel blockers may be explained by the synergetic effects on D2 receptors. Studies have indicated that (−)-OSU6162 exerts stabilizing effects on serotonergic transmission, partial agnostic action on 5-HT2a receptors (250, 251), and two clinical trials have indicated an antidepressant effect of (−)-OSU6162 (260, 263). Besides interaction on the serotonergic pathway, interaction may also occur with (−)-OSU6162 on the dopaminergic pathway where SSRIs can cause a decrease in striatal D2 receptor availability (329). Further, beta-blockers interact with the D2 receptor (330) and calcium-channel blockers reduce the striatal D2 receptor binding potential (331, 332). Hence, certain concomitant medications can cause a shift in optimal mode of action for (−)-OSU6162 dependent on the individuals dopaminergic tone, since the effect of (−)-OSU6162 is dopaminergic tone-dependent (246), and should be explored further.

In a review by Murray and Stoessl (328), the authors stated that emphasis should be placed on the potential of placebo effect to enhance pharmacological interventions. But it is a challenge to entangle the unique contribution of the placebo effect, antidepressants, beta- or calcium-channel blockers and (−)-OSU6162 when we did not include a no-treatment control. That is, evaluation of efficacy requires placebo, but comparison for clinical effectiveness is the presence of a no-treatment group.

In paper II, we demonstrated a close relationship between fatigue and depression. Further, in paper III we found an overall improvement in both fatigue and depressive symptoms, as well as a correlation of plasma concentration of (−)-OSU6162 and improvement in fatigue and depressive symptoms, in combination with enhanced efficacy of (−)-OSU6162 with concomitant use of antidepressant - Is it possible that improvements in fatigue was mediated by a decrease in depressive symptoms? The results from previous studies suggest otherwise. Wendenbourg et al. (221) found educational and CBT-based treatment to reduce fatigue in MS patients, but that was not the case for depressive symptoms. Ponsford and colleagues (333) found fatigue to precede depression rather than being secondary to mood disorders in TBI patients. Previous pharmacological trials have shown fatigue to persist despite reduction of depressive symptoms in stroke patients (240, 242, 334). One can speculate if fatigue and depression can be the results of the same pathophysiological underpinning, but with mediators and moderators leading to different outcomes in different individuals (biopsychosocial stress model). Taken together, fatigue and depression should be viewed and treated as distinct constructs.

Further, fatigue (as indicated by FSS mean score) was distinctly improved only in patients with full return to previous workload (complete RTW) upon treatment with (−)-OSU6162. Nilsson et al. (263) found a significant decrease in fatigue (as indicated by MFS sum score) in patients with highest levels of sick leave upon (−)-OSU6162 treatment. We found no significant group differences for the MFS in relation to RTW. Since FSS measure the impact of fatigue on daily life, an decrease of negative behavioral consequences of fatigue may be more obvious for those with complete RTW who strain their energy levels the most. This would also be in accordance with the finding of highest degree of improvement on FSS item 7 ("Fatigue interferes with carrying out certain duties and responsibilities") in the (−)-OSU6162 group.

In summary, our RCT is hitherto the largest clinical trial investigating the efficacy of (−)-OSU6162, and to our knowledge the first to study the effect of this substance on sequelae after aSAH. In fact, the present study is the only pharmacological intervention study with fatigue as primary outcome measure that has been conducted in the aSAH population until now. Overall, fatigue and other sequelae after aSAH were similarly alleviated by treatment with (−)-OSU6162 and placebo, suggesting that the strong placebo response may be exploited in the development of non-pharmacological treatment programs for post-aSAH fatigue.

5.7 General methodological considerations

5.7.1 Representatively and generalizability

In paper I, the study covered the largest geographical area of the four Regional Health Authorities in Norway and included the entire range of aSAH severity. However, we excluded patients with severe impairments in cognition or communication (<15%), thereby limiting the generalizability (i.e., external validity) of our prevalence estimate not to reflect the overall aSAH population. Further, we included patients over a long period from ictus which may have introduced uncertainties regarding the etiology of fatigue. On the other hand, we found fatigue to be relatively stable over this wide time frame and therefore adding to the growing literature that understands fatigue as a long-lasting symptom if not alleviated in early phase.

The strict selection of participants based on a range of inclusion and exclusion criteria for our phase II RCT should be considered when interpreting our findings in paper II and III. Even though we included participants over the entire specter of aSAH severity (even more in poor grade compared to the excluded patients), our study participants were all deemed as "good outcome" (mRS 0-2). Further, the included patients were younger compared to the excluded patients and highly educated (49% had completed undergraduate or graduate school). Besides the explicit exclusion criteria (as listed in section 3.3.2) that obviously had the potential to limit the generalizability of our findings, there might be other unknown forms of selection bias that were present at the individual study level since the RCT was quite comprehensive. Personal finances could have played a part in deciding to participate since many had to travel over long distances, even though we informed that one could apply for economical compensation afterwards. Many of our aSAH survivors declined further participation due to the long travel distance in combination with multiple times of assessment, saying they were too fatigued. As such, the study participants may not be representative of aSAH patients with lower education level, with a poor financial situation, extreme degree of fatigue, and/or those living in more rural areas. It should also be mentioned that Norway is a welfare state that provides healthcare and social security benefits for all its citizens and the numbers regarding return to work may have limited generalizability to countries outside Scandinavia.

5.7.2 Sample size

Sample size is an ever-recurring issue when generalizing the findings from studies of aSAH – a relative infrequent disease with high mortality. The sample size calculation was determined on the basis of available literature (12, 132, 277) assessing the variability of FSS scores in the aSAH population. Our calculation of 34 patients in each group was comparable to the calculation by Berginström et al. (313) that defined 30 patients in each group to be adequate. With an estimated drop out rate of 15%, a total sample size of 80 patients were required. From baseline to the follow-up 8 weeks after the end of treatment, only five participants dropped out (5.2% drop out rate). However, data were analyzed according to the intention-to-treat principle as recommended by the CONSORT guidelines and according to criteria for full analysis set as described in the statistical analyses plan. Hence, effort was made to reduce the

risk of bias and increase the chances of drawing firm conclusions about the efficacy of (−)-OSU6162.

Even though our study is hitherto the largest clinical trial for investigating (−)-OSU6162, a larger sample size could have shown a clearer difference between treatment groups when investigating a phenomenon that fluctuates according to contextual demands. Also, the number of participants were moderate or low when exploring results in subgroups.

5.7.3 Measurements and assessment

The chosen cut-off point for the FSS (mean score ≥4) has been commonly used across different study populations, because fewer than 5% of healthy controls rated their fatigue above this level in combination with up to 90% of patients with medical disorders experienced fatigue according to this criteria (188). However, Lerdal et al. (111) has proposed FSS mean ≥5 as a more proper cut-off stating that the original cut-off point is too liberal resulting in over-estimation of fatigue prevalence. Nevertheless, if the presence of fatigue was to be recalculated according to the cut-off by Lerdal et al., our prevalence estimate of post-aSAH fatigue (ie., 53.9%) would still exceed the frequency seen in the general population.

However, the mode of FSS assessment by telephone interview (paper I) might be a limitation of our study when making comparisons to other studies. Most commonly, the items of FSS are evaluated in a paper-and-pencil format directly by the patient. In our setting, if a patient expressed difficulties remembering the Likert-scale (1= complete disagree, 7=complete agree) they were asked to write it down while giving oral responses. Since all FSS items are formulated in a negative direction, i.e. an “agree” response is indicative of more fatigue, this might possibly have led to a stronger tendency to agree among patients with cognitive impairments.

Further, is the FSS sensitive to detect change over time when used as primary outcome measure in a treatment study? And does it makes sense to measure fatigue 6 times over a 20 week period? Sensitivity to change and frequency of assessment poses great challenges, since fatigue in its inherent nature fluctuates and changes according to internal and external demands. There are no psychometric data on the responsiveness of FSS, hence there is limited knowledge of the degree of error when measuring changes in fatigue over time (165). Maybe

it makes more sense to talk about the minimal clinically important difference (335) for FSS, defined as the smallest difference in the fatigue outcome which patients perceive as beneficial? In a systematic review by Nordin and colleagues (336), minimal important difference for FSS was found to be between 0.5 and 1.2 points for global change, which corresponds to a change of 7.1% to 25.7% of maximum FSS mean score. Our criteria of clinical change by 1.5 point (i.e., 21.4% change of FSS mean score) might have been too conservative. The pitfall of the latter is to wrongly categorize patients as non-responders to a pharmacological treatment that is effective. Our findings of a significant correlation between improvement in FSS score and (−)-OSU6162 plasma concentration in those using 60 mg/day (at week 8 of treatment) might be in favor of this interpretation. However, this would not diminish the response of the placebo group, therefore not changing the main findings of no group difference in treatment.

6 Conclusions and implications

6.1 Conclusions

- Fatigue is a frequent and long-lasting symptom in the chronic phase after aSAH.
- Independent risk factors for the development of fatigue after are nicotine use leading up to the IA rupture, reduced consciousness (GCS <14) at admission and the presence of severe vasospasm during management of aSAH. We postulate that fatigue and the aforementioned predictors are related to a cascade of pathophysiological events that have pro-inflammatory cytokines causing dopamine imbalance as a common denominator.
- Fatigue after aSAH is a multidimensional phenomenon perceived as one of the most disabling symptoms after hemorrhage and best characterized as a mental form of fatigue exacerbated by stress and closely related to motivation.
- Fatigue after aSAH and depression are strongly associated, but the incomplete overlap suggest that they are best understood as separate constructs.
- Fatigue after aSAH is strongly related to reduced HRQoL and partially to low rate of RTW, but not to neurological status nor cognitive functioning.
- (−)-OSU6162 is not superior to placebo in alleviating fatigue after aSAH. A strong placebo response may be exploited in the development of non-pharmacological interventions.

6.2 Implications for clinical practice and future research

The aSAH survivors are “the forgotten minority” within the stroke population. The hemorrhage is described as an event, but the illness should be viewed as a long and weary transition from the acute to the chronic phase. Fatigue after aSAH is a frequent symptom and best understood as a chronic condition beyond 1 year after hemorrhage. Despite a wide range in prevalence estimates, post-aSAH fatigue is still common if the lower end of its occurrence range is accepted. Consequently, healthcare professionals should be aware and be able to discuss this topic with patients who is at risk or report fatigue at the regular follow-up time 3 months after aSAH (outpatient clinic).

Post-aSAH fatigue poses devastating health consequences not only for the individual, but for families and communities. After discharge from the hospital, the patient is at the mercy of his or her general practitioner. Patients are only randomly referred to rehabilitation institutions at the specialist health service level. The aSAH survivors should be screened for common problems seen after aSAH (fatigue, cognitive and emotional problems) in the early phase (2-4 months) after discharge, during sick leave (<12 months after hemorrhage) and later on if a patient is entitled work assessment allowance (AAP from the Norwegian Labour and Welfare Administration, NAV, ≥12 months after hemorrhage). From my clinical experience, most patients are primarily oriented towards appreciation of survival during the early stage. Most of the patients can walk, talk and move their body before discharge to home. However, emotional and cognitive difficulties, fatigue, gaps in knowledge about aSAH, unrealistic expectations and issues about own mortality – invisible difficulties – are issues that become more prominent when resuming to routines and everyday life.

Health care support should be offered to the patient following discharge and beyong regular follow-up at 3 months after hemmorhage. We did not find (−)-OSU6162 to be an effective treatment for fatigue after aSAH, but we demonstrated a strong placebo effect. During the many visits required in the RCT, we offered information, reassurance, and normalization – factors that can shape a patients expectations and perception of symptoms. Is it possible to ethically apply the placebo effect in a rehabilitation setting? The placebo effect is often viewed as unscientific and illegitimate. But as stated by Kaptchuk and Miller (315), medicine's goal is to heal, which can include cure, control of disease, symptom relief or comfort. When no cure is available at the moment, the ultimate mission should be to relieve unnecessary suffering. Therefore, though placebo rarely cure it may provide relief. A supportive, attentive and empathetic health care creates a "therapeutic bias" that can predispose patients toward reduced symptom severity and lessened reactivity to underlying pathophysiology, making them less disturbed or perturbed. Placebo effects can help explain mechanistically how clinicians can be therapeutic agents in the ways they relate to their patients. These mechanisms may be some of the active ingredients in CBT-based approaches and educational interventions that also seems like promising interventions for fatigue symptom burden.

Future studies should aim for a clear definition/operationalization of fatigue and common PROMS, thereby making the comparison of findings between studies more feasible. Further, it seems pertinent to standardize an "objective" fatigue outcome measure, for example the

development of a computerized test that can discriminate between fatigued and non-fatigued patients. But even more promising would be to find biomarkers of high sensitivity and specificity to evaluate and continuously assess in longitudinal studies where baseline is at admission at the hospital for aSAH and where last point of assessment would be at least 1 year after ictus. Interleukin**s,** a group of cytokines, seems like promising candidates.

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8 Appendix

8.1 In-depth description of study procedures

A detailed description of physical and neurological examination at week 0, 8, and 12, and at follow up 8 weeks after treatment.

Physical examination was documented as follows:

- Coronary: normal/abnormal (specify)
- Pulmonary: normal/abnormal (specify)
- Abdominal: normal/abnormal (specify)
- Skin: normal/abnormal (specify)

Neurological examination was documented as follows:

- Cranial nerves: normal/deficit/worsened/improved (specify)
- Sensibility: normal/reduced/worsened/improved (specify)
- Speech: normal/dysphasia/worsened/improved (specify)
- Gait: normal/unsteady/worsened/improved – (specify any aids)
- Coordination: normal/ataxia/worsened/improved (specify)
- Babinski reflex: up/neutral/down
- Tone: normal/spasticity/rigidity (specify)
- Urinary function: normal/urge/retention/worsened/improved
- Motor function/strength was tested for right and left upper extremity as well as for right and left lower extremity and described by the appropriate number:

0	No movement
1	Barest flicker of movement of the muscle, though not enough to move the structure to which it's attached.
2	Voluntary movement which is not sufficient to overcome the force of gravity.
3	Voluntary movement capable of overcoming gravity, but not any applied resistance.
4-	Significantly reduced, overcomes slight resistance (25% strength)
4	Moderatly reduced, overcomes moderate resistance (50% strength)
4+	Slightly reduced, overcomes strong resistance (75% strength)
5	Normal strength

- Reflexes was tested in the right and left side: Biceps, triceps, brachioradialis, patellar, Achilles. Reflexes were described by the appropriate number for intensity of muscle contraction:

0	No evidence of contraction
1+	Decreased, but still present (hypo-reflexic)
2+	Normal
3+	Super-normal (hyper-reflexic)
4+	Clonus: Repetitive shortening of the muscle after a single stimulation

8.2 Prescreening form

Demographical data (name, sex, birth date and social security number, contact information), aSAH-related information (time of ictus, aneurism localization and type of repair method) was found in the patients journal. We asked questions about language/mother tongue, estimated level of education and type of education/professional, work status (0-100%) before and after aSAH, somatic diseases before and after aSAH (specifically about hydrocephalus, epilepsy, serious illness related to the brain, current drug abuse, liver or kidney disease), psychiatric diagnosis/psychological problems before and after aSAH, and use of over-the-counter and prescription drug. In addition, all women were asked if they were currently pregnant or were planning on becoming pregnant or currently breastfeeding if being in the age of childbearing potential, otherwise if they had researched menopause or used adequate contraceptives. All men were asked if they would consent to use condom under the study period and the three subsequent months after intake of last dosage of study drug if enrolled in the study.

At last, the Fatigue Severity Questionnaire (FSS) was evaluated with the patient. If the mean score was ≥4, they were invited to join the RCT. If the patient answered yes and was interested in participation, they were sent written information (the consent form) by mail.

8.3 Viedoc

At visit 1 (screening), every patient were registrered as a participant by the team investigator in our electronic data capture. The team investigator and PhD candidate informed the patient about PROMs and our intent to assess their experience during and after treatment. Most patients opted for the electronically version, but two patient wanted to fill out the PROMs on paper. The PhD candidate would instruct the patients in how to answer PROMS and the electronic version will be described in detail.

The Viedoc Clinical (used by team investigator) allowed for the registration of a ViedocMe account (see Figure 11) for the specific patient (linked to mobile phone number and e-mail address for reminders). A username and password would be generated by the Viedoc Clinical system and were handed as written information to the patient.

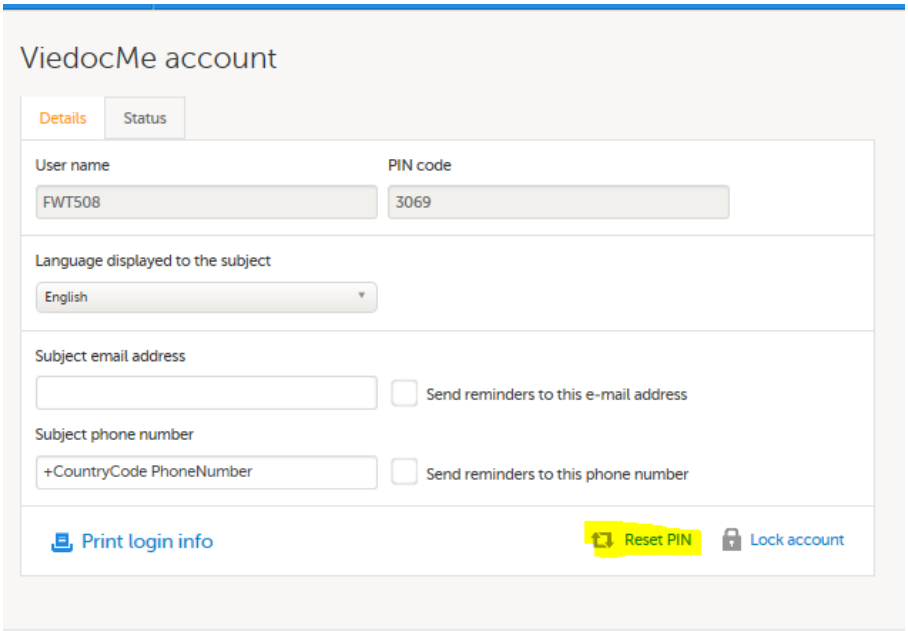

Figure 11. Registration of a ViedocMe account for each participant in the RCT.

On site, the patient was instructed to log into their account for the first time and shown how to navigate in the graphical user interface of ViedocMe. All patients completed 1 out of 10 PROMS (ie., the FSS) while under supervision by the PhD candidate. The patients were instructed that there was no right or wrong answers, and to choose the alternative that was

most suitable for them according to the time interval specified in the instruction of the different PROMS if they did not find the perfect alternative to match their experience. During the study, team investigators would monitor the progress by the presence of a green checkbox for a specific PROM (see Figure 12).

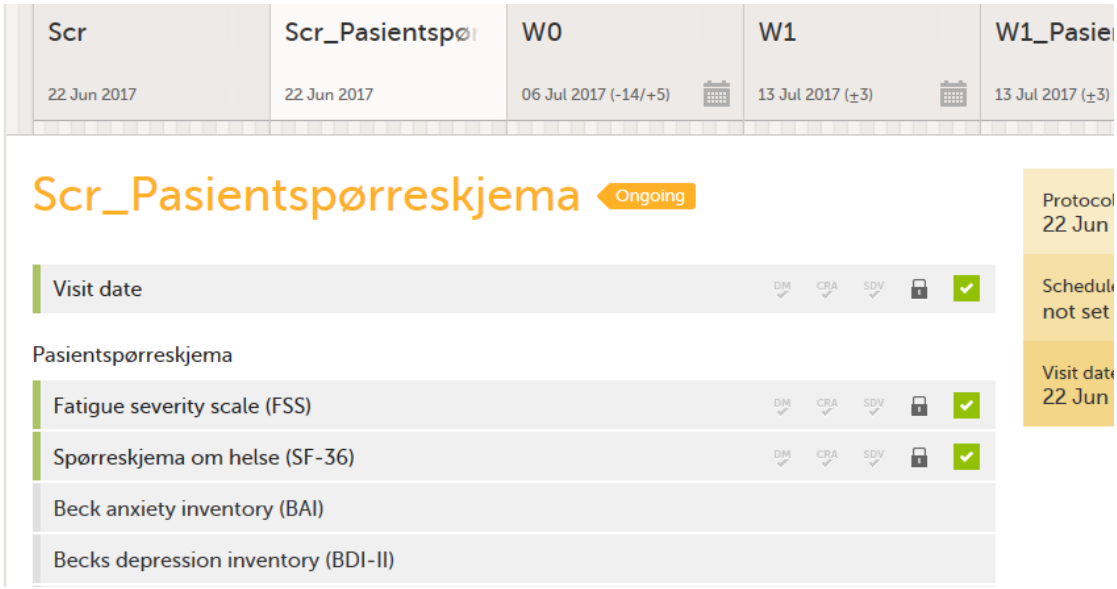

Figure 12. Interface of ViedocMe that illustrates progress in answering PROMs.

During the completion of a specific PROM, the patient had to answer all questions before the system allowed for continuation. If a question was omitted, mostly by fault, the system would also alert the patient of which question that must be answered. In this way, the possibility for missing data for PROMS was reduced to a minimum (see Figure 13). The most critical point was time of completion. That is, the PROMS could not be answered before or after the time slot allowed for completion, a period of time predefined by the time of entry.

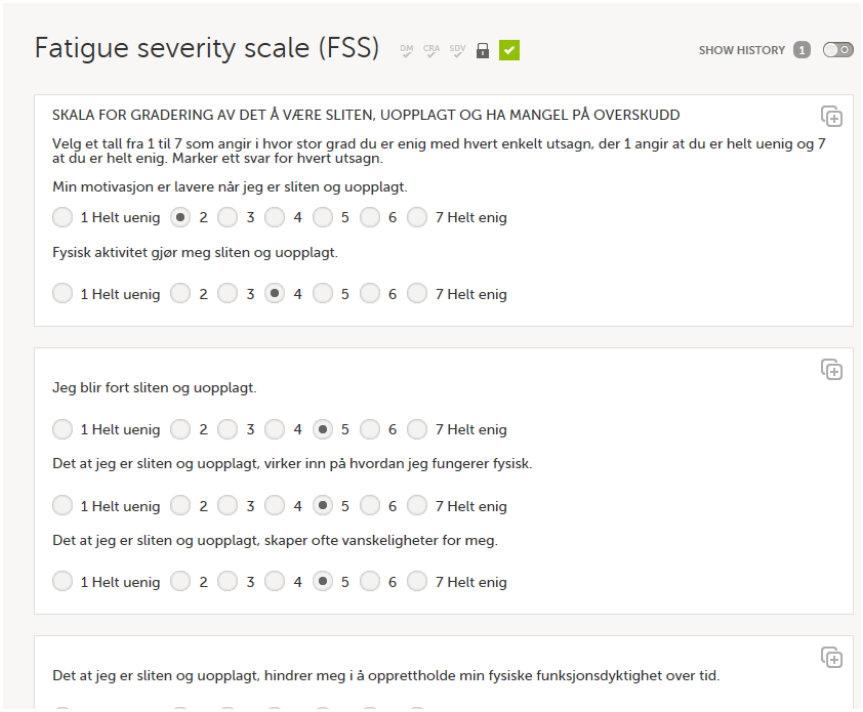

Figure 13. Illustration of interface when answering the Fatigue Severity Scale in ViedocMe.

8.4 Paper I-III

I

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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ANEURYSM

Prevalence and predictors of fatigue after aneurysmal subarachnoid hemorrhage

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Abstract

Background Fatigue is a common and disabling sequel after aneurysmal subarachnoid hemorrhage (aSAH). At present, prevalence estimates of post-aSAH fatigue in the chronic phase are scarce and vary greatly. Factors from the acute phase of aSAH have hitherto barely been associated with post-aSAH fatigue in the chronic phase.

Methods Prospective study assessing prevalence of fatigue using the Fatigue Severity Scale (FSS) in patients who were living independently 1 to 7 years after aSAH. We compared demographic, medical, and radiological variables from the acute phase of aSAH between patients with and without fatigue (FSS ≥ 4 versus < 4) and searched for predictors of fatigue among these variables applying univariable and multivariable regression analyses.

Results Of 726 patients treated for aSAH in the period between January 2012 and December 2017, 356 patients completed the assessment. The mean FSS score was 4.7 ± 1.7, and fatigue was present in 69.7%. The frequency of patients with fatigue did not decline significantly over time. Univariable analysis identified nicotine use, loss of consciousness at ictus (LOCi), rebleed prior to aneurysm repair, reduced consciousness to Glasgow Coma Scale (GCS) < 14, large amounts of subarachnoid blood, the presence of acute hydrocephalus, and severe vasospasm as factors that were significantly associated with fatigue. In multivariable analysis, nicotine use, reduced GCS, and severe vasospasm were independent predictors that all more than doubled the risk to develop post-aSAH fatigue.

Conclusions Fatigue is a frequent sequel persisting several years after aSAH. Nicotine use, reduced consciousness at admission, and severe vasospasm are independent predictors of fatigue from the acute phase of aSAH. We propose inflammatory cytokines causing dopamine imbalance to be a common denominator for post-aSAH fatigue and the presently identified predictors.

Keywords Aneurysmal subarachnoid hemorrhage · SAH · Fatigue · Prevalence · Predictors

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Abbreviations

ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
aSAH	Aneurysmal subarachnoid hemorrhage
ATP	Adenosine triphosphate
CT	Computed tomography
CTA	Computed tomography angiography
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
DCI	Delayed cerebral ischemia
FSS	Fatigue Severity Scale
GCS	Glasgow Coma Scale
HH	Hunt and Hess Scale
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
IVH	Intraventricular hemorrhage

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ICP	Intracranial pressure
LOCi	Loss of consciousness at ictus
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
PTSD	Post-traumatic stress disorder
TCD	Transcranial Doppler ultrasonography

Introduction

Fatigue can be characterized by "a feeling of lack of energy, weariness, and aversion to effort" [32]. Currently there is no agreed-upon definition or operationalization of fatigue, partly a result of its complex and multidimensional nature. Fatigue is the most prominent sequel in a cluster of residual symptoms after aneurysmal subarachnoid hemorrhage (aSAH) [34]. Although being highly frequent in the early phase [36, 41], post-aSAH fatigue is also present several years after the ictus [7, 44] and it is a debilitating symptom that has a significant impact upon quality of life and the ability to return to work [38, 43]. Estimates of fatigue prevalence after aSAH vary between 31 and 90 % [28]. This large variability may be related to heterogeneity in study population, timing of assessment after the hemorrhage and methods of assessment for fatigue.

Since fatigue is common in many neurological disorders [9], there may be a range of different underlying neurobiological mechanisms. The pathophysiology of fatigue after ischemic and hemorrhagic stroke remains unclear [11] and the knowledge of aSAH-related factors associated with post-aSAH fatigue is even more limited. Only a small number of studies have examined multiple clinical predictors and their relationship with post-aSAH fatigue [7, 26, 37, 41]. In combination with relative small sample sizes in previous studies, factors associated with post-aSAH fatigue have not been comprehensively evaluated.

Subjects and methods

Subjects

The current study was part of the pre-screening for a double-blind, randomized, placebo-controlled study investigating the effect of OSU6162 in the treatment of fatigue and other neuropsychological sequelae after aSAH (http://www.clinicaltrials.gov. Unique identifier: NCT03209830) approved by Health Research Ethics (REC, reference: 2016/2214). Patients (≥ 18 years) that had suffered aSAH at least 1 year earlier and who were treated for their aSAH at our department between January 2012 and December 2017 were contacted. Patients who agreed to participate were interviewed by phone and gave an oral informed consent. Patients living permanently in an institution and those not speaking adequately Norwegian were excluded. The data collection protocol was approved by the institutional review board. The study data that support the findings of this study are available from the corresponding author on reasonable request.

Measures

Fatigue

Fatigue in the chronic phase (≥ 1 year) after aSAH was assessed using the Norwegian version of the Fatigue Severity Scale (FSS) [27, 30] which consists of nine statements about the impact of fatigue on daily life; each statement is scored on a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). The total FSS score is the mean of the item scores. A mean score of 4 or more is considered outside the range of healthy controls [27] and indicates a moderate to high impact of fatigue on daily living.

Predictors

Data on demographics (age and sex), medical condition at admission, and clinical course during the acute phase of aSAH were obtained from our institutional quality registry. We registered nicotine use at the time of ictus, if there was an abrupt LOCi including seizures, rebleed before aneurysm repair, clinical grade just prior to aneurysm repair or prior to intubation in patients admitted intubated (Hunt and Hess Scale [HH] [21] and Glasgow Coma Scale (GCS) [23]), aneurysm location, and the method of aneurysm repair. From the diagnostic computed tomography (CT), we scored the presence of intraparenchymal hemorrhage, the amount of subarachnoid blood (modified Fisher grade [18]), and the amount of intraventricular blood (modified LeRoux score [29], where no intraventricular blood was scored as "0"). Furthermore, we registered if the patient was treated for acute hydrocephalus (need of external drainage of CSF), or for chronic hydrocephalus (implanted shunt). All patients underwent a CT/CT angiography (CTA) on the first day after aneurysm repair and on day 5 in intubated patients and on day 7 in awake patients. Transcranial Doppler ultrasonography (TCD) was performed from day 4 and at regular intervals. We scored the presence of severe vasospasm if CT angiography scans showed a > 50% diameter reduction in one or several vessels and/or TCD showing a Lindegaard ratio [31] > 6. The acquisition of a new cerebral infarction, including those that were procedure-related, was evaluated from CT scans performed during the primary hospital stay or from magnetic resonance imaging (MRI) if performed.

Statistical analysis

Patient characteristics are presented as mean values with standard deviation (SD) or proportions. Differences in continuous variables between groups were tested using independent sample *t* test or one-way ANOVA. The chi-square test for contingency tables was used to detect associations between categorical variables. To evaluate the frequency of fatigue across time intervals in years since ictus, a Mantel-Haenszel test for trend was performed. Univariable and multivariable logistic regression analyses were performed to identify possible predictors of fatigue (FSS ≥ 4): LOCi (yes or no), rebleed (yes or no), Hunt and Hess scale (1–3 or 4–5), modified Fisher scale (0–2 or 3–4), modified LeRoux score (0–5 or 6–16), severe vasospasm (yes or no), acute hydrocephalus (yes or no), chronic hydrocephalus (yes or no), intracerebral hemorrhage (ICH) (yes or no), and cerebral infarction (yes or no) were dichotomized. Aneurysm location, GCS, and nicotine use were entered by using 3 dummy variables. Any variable with $p < 0.05$ in the univariable analysis was considered a candidate for the multivariable model. Subsequent multivariable logistic regression analyses with manual backward elimination were performed. The associations between potential predictors and fatigue were quantified by odds ratio (OR) with 95% confidence interval (CI). Multivariable analyses were preceded by estimation of correlation between predictors. Two-tailed *p* values of less than 5% were considered statistically significant. All statistical analyses were performed using the IBM SPSS statistics version 25.0 (IBM SPSS Inc., Armonk, NY: IBM Corp).

Results

A total of 726 patients were admitted for non-traumatic aSAH between January 2012 and December 2017. Figure 1 shows the flow chart of eligible and included patients. A total of 655 patients received active treatment. In this group, 138 died, 69 were severely disabled and/or resided in a nursing home, 30 were living outside Health Region South East, and one was younger than 18 years. Therefore, 417 were eligible for telephone interview, of whom 356 (85%) participated in the study. We excluded 21 patients with insufficient skills in Norwegian, 30 patients were unable to be traced or did not answer, and 10 patients declined participation. The characteristics of the 356 included patients are displayed in Table 1.

Prevalence and duration of fatigue

The mean FSS score was 4.7 (SD, 1.7) and fatigue (FSS ≥ 4) was present in 248 patients (69.7%) (Table 1). Figure 2 shows the prevalence of fatigue in relation to time passed since the aSAH. From 1 and up to 7 years after the ictus, fatigue was present in 74%, 74%, 61%, 77%, 65%, and 60%, respectively. Even though there seemed to be a tendency towards decline of fatigue as a function of time, the Mantel-Haenszel test for trend demonstrated that fatigue was stable over time (p 0.057).

Predictors of fatigue

Results of the univariable analyses on predictors linked to the acute phase of aSAH (demographic, medical, and radiological data) are presented in Table 2. Nicotine use (OR 2.49, 95% CI 1.50–4.14; $p < 0.001$), reduced consciousness to GCS 13–9 (OR 2.46, 95% CI 1.21–4.98; $p = 0.013$) and GCS 8–3 (OR 2.30, 95% CI 1.16–4.56; $p = 0.017$), larger amount of subarachnoid blood (modified Fisher scales 3 and 4: OR 1.86, 95% CI 1.18–2.94; $p = 0.008$), LOCi (OR 2.04, 95% CI 1.26–3.30; $p = 0.004$), rebleed before aneurysm repair (OR 3.05, 95% CI 1.04–8.95; $p = 0.043$), severe vasospasm (OR 2.49, 95% CI 1.21–5.12; $p = 0.013$), and acute hydrocephalus (OR 2.08, 95% CI 1.30–3.32; $p = 0.002$) were identified as statistically significant predictors of fatigue. The mean FSS was significantly lower in never nicotine users (4.20 ± 1.80) than in former users (4.65 ± 1.55) and current users (4.91 ± 1.61) ($p = 0.002$; Fig. 3, left). Likewise, the mean FSS was significantly lower in patients with GCS 15–14 (4.48 ± 1.79) than in those with GCS 13–9 (4.91 ± 1.44) and those with GCS 8–3 (5.08 ± 1.40) ($p = 0.020$; Fig. 3, right).

The final multivariable regression model is presented in Table 2, right column, and identified nicotine use, GCS < 14, and severe vasospasm as independent predictors which approximately doubled the risk to develop fatigue after aSAH: nicotine use (OR 2.10, 95% CI 1.31–3.39; $p = 0.002$) as compared with former and never nicotine use, patients in GCS 13–9 (OR 2.49, 95% CI 1.21–5.14; $p = 0.014$) and GCS 8–3 (OR 2.13, 95% CI 1.03–4.38; $p = 0.040$) as compared with patients in GCS 15–14, and patients with severe vasospasm (OR 2.30, 95% CI 1.10–4.82; $p = 0.028$) as compared with patients with less severe or no vasospasm.

The interwoven relationship of clinical variables related to aSAH is illustrated in Fig. 4. We focused on the presently identified predictors of post-aSAH fatigue and how they possibly may culminate in processes leading to or facilitating the development of fatigue.

Discussion

The core finding in the present study was that the prevalence of fatigue in the chronic phase after aSAH was 69.7% and remained stable over at least 1 to 7 years after the hemorrhage. Nicotine use, reduced consciousness at admission, and severe vasospasm in the acute phase were independent predictors of fatigue.

Table 1 Characteristics of patients with aSAH (n = 356)

	n	%
Mean age at ictus, years	55.7 ± 12.5	
Sex, male	115	32.3
Predictors		
Aneurysm location		
ACoA/ACA	148	41.6
MCA/ICA	154	43.3
Vertebrobasilar	54	15.2
Treatment		
Spontaneous aneurysm thrombosis	2	0.6
Endovascular	194	54.5
Surgical	160	42.7
Hunt and Hess (HH)		
HH 1–3	284	79.8
HH 4–5	72	20.2
Glasgow Coma Score (GCS)		
GCS 15–14	236	66.3
GCS 13–9	59	16.6
GCS 8–3	61	17.1
Modified Fisher		
0–2	169	47.5
3–4	186	52.2
Modified LeRoux		
0–5	301	84.6
6–16	54	15.2
Nicotine use		
Current	191	53.7
Former	56	15,7
Never	106	29,8
Loss of consciousness at ictus (LOCi)	146	41.0
Rebleed before aneurysm repair	30	8.4
Severe vasospasm	60	16.9
Acute hydrocephalus	239	67.1
Chronic hydrocephalus	83	23.3
Intracerebral hemorrhage	72	20.2
New cerebral infarction	97	27.2
Fatigue		
Mean follow-up time after aSAH in months (SD); range in months	37.6 (23.9); 12–81	
Fatigue Severity Scale (FSS)		
Mean FSS (SD)	4.7 (1.7)	
Clinical fatigue (mean FSS ≥ 4)	248	69.7

Prevalence of post-aSAH fatigue

Our prevalence of 70% is consistent with previous studies that assessed the prevalence of fatigue by means of the FSS questionnaire in patients surviving aSAH [28]. However, other studies that used single questions to assess fatigue reported a much more widespread prevalence [28]. The variance in prevalence is not surprising since there is no "gold standard" or objective measure of fatigue, and the lack of consensus regarding the definition of fatigue is therefore a challenge for allowing consistent measures [13]. Self-report measures of fatigue have major limitations, especially questionnaires that fail to regard fatigue as a multidimensional state with cognitive and emotional/psychological components. Another factor contributing to varying results regarding prevalence of fatigue is low sample size. To the best of our knowledge, the 356 aSAH patients we presently examined comprise by far the largest cohort investigated on this topic to date.

Timely evolvement of post-aSAH fatigue

Previous longitudinal studies show a consistency in fatigue levels over time [3, 19, 26, 39], where no improvement of fatigue was found in studies with follow-up assessment up to 4 years after the ictus [3, 19]. In line with our findings, other cross-sectional studies [6, 7, 43] have shown a high prevalence of fatigue (47–66%) up to 10 years after the ictus. A systematic review by Kutlubaev et al. [28] reported a higher frequency of fatigue less than 1 year compared with more than 1 year after the ictus (73.6% and 50.7%, respectively), which they postulate can be explained by different mechanisms driving fatigue as a function of time since ictus. On the other hand, in a meta-analysis by Cumming et al. [10], a marked between-study variability in the estimates of fatigue prevalence was not accounted for by timing of assessment after stroke. The authors therefore concluded fatigue to be persistent across time. Hitherto, there are insufficient data to draw any firm conclusions regarding time course; however, there are strong indications that fatigue remains relatively stable after the acute phase. Our data were acquired in patients where the hemorrhage was at least 1 year ago and support the notion that fatigue beyond 1 year is best understood as a chronic condition.

The dopamine imbalance hypothesis

Not only the definition and quantification of fatigue is challenging, also the underlying biomedical mechanisms remain unclear. Since central fatigue [8] is seen in a wide specter of diseases that share some kind of proinflammatory mechanism, the hypothesis of cytokine-induced inflammation-mediated fatigue has emerged [4, 25, 40]. Inflammatory cytokines have an effect on dopamine release and proper function in the striatum [17]. Such findings support the notion that inflammatory cytokines lead to dopamine imbalance [14] in the dopaminergic pathways, namely the mesocorticolimbic and nigrostriatal systems. The dopamine imbalance hypothesis states that

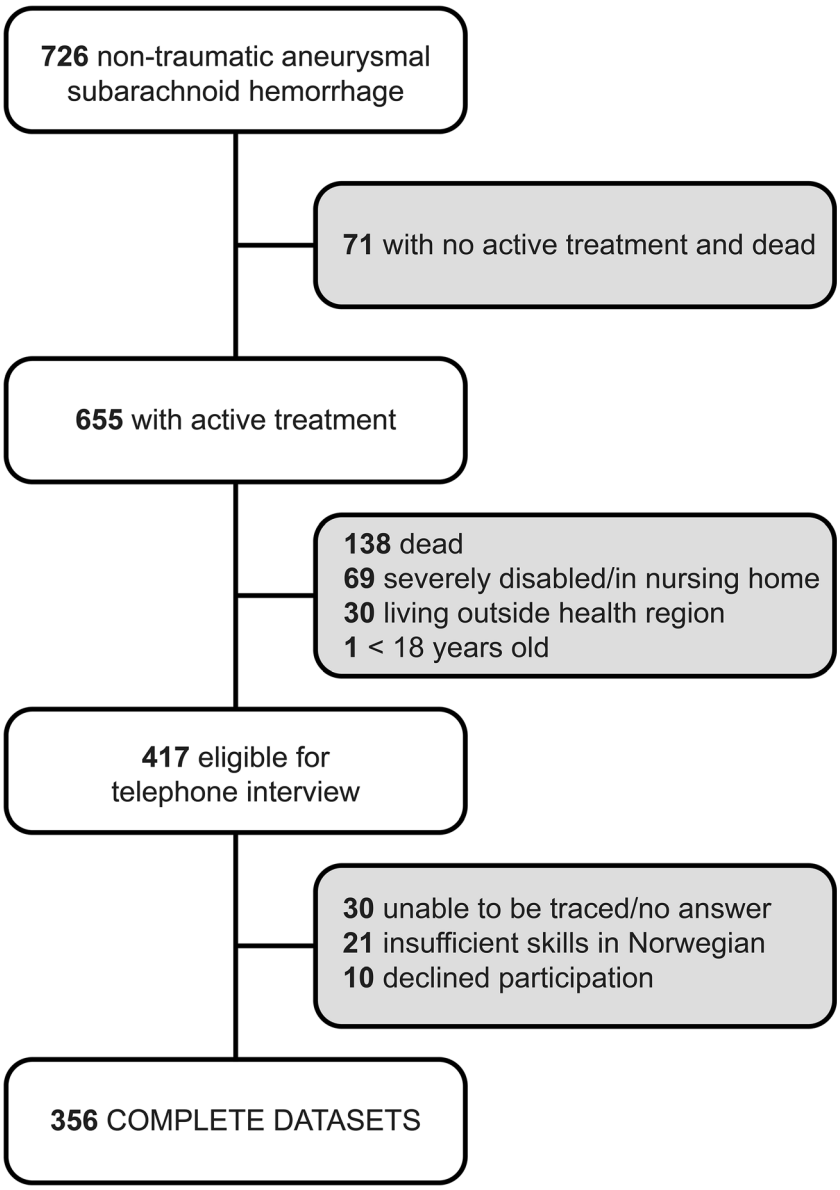

Fig. 1 Patient enrollment

dopamine may play an important role in the perception of fatigue because it is central for cognition, motivation, and effortful behavior [1, 14]. In fact, individuals with high levels of fatigue have reduced mesocorticolimbic connectivity [16]. Dopamine is often referred to as the "reward neurotransmitter," delicately balancing if a reward is worth the effort [1]. The effect of dopamine follows an inverted "u" shape, with optimal effect on the top of the curve; i.e., fatigue can be caused by too little as well as too much dopamine [14].

Predictors of post-aSAH fatigue

These hypotheses are relevant in relation to the presently identified predictors of fatigue. Our strongest predictor was use of nicotine. Nicotine addiction is created and maintained in the mesocorticolimbic system where it binds to nicotinic acetylcholine receptors and increases the firing rate and phasic bursts in midbrain dopamine neurons [2]. Chronic nicotine use leads to neuroadaptation and changes in dopamine homeostasis [2], possibly shifting dopamine levels to a point on the inverted "u" curve that promotes the development of fatigue. Nicotine is also a well-established risk factor for aSAH and clinical symptomatic vasospasm and delayed ischemic neurologic deficit in the course of aSAH [12]. Furthermore, nicotine aggravates the post-ischemic inflammatory response and thereby increases brain infarction size [5]. Common background factors for individuals with fatigue and nicotine users, like socio-economic factors and passive coping style, should also be considered.

Despite the large impact of nicotine on the same dopaminergic pathways that seem to be crucial in the development of fatigue, no other studies have investigated this correlation. To

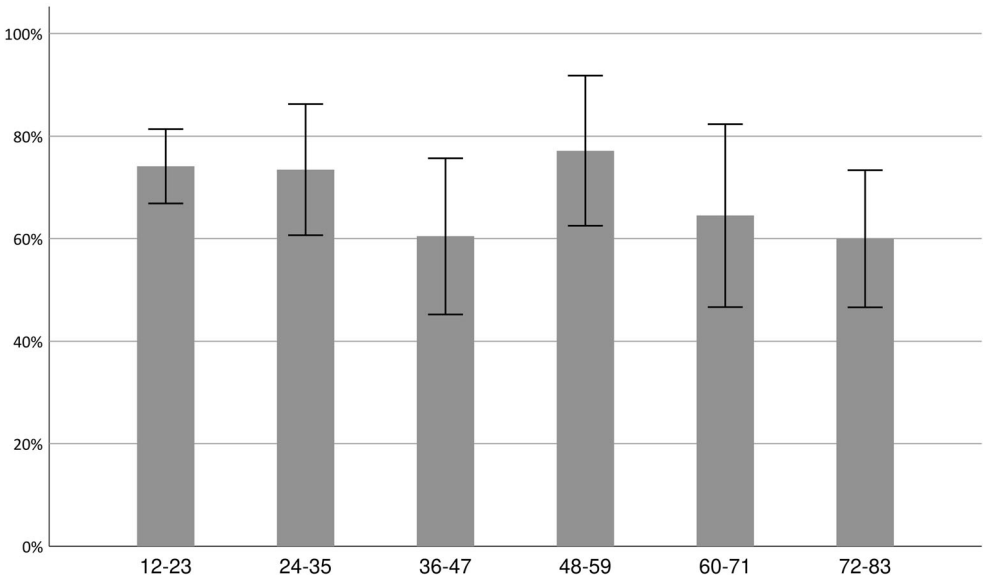

Fig. 2 Percentage of patients with fatigue in relation to months passed since ictus

our knowledge, merely four previous studies [7, 26, 37, 41] have looked at the relationship between acute SAH-related factors and fatigue in the chronic phase, where three of the studies investigated their patients within 14 months after the hemorrhage. Rödholm et al. [41] found no significant association between fatigue (as defined by astheno-emotional disorder) and reaction level upon admission, amount of subarachnoid blood, or acute hydrocephalus. Passier et al. [37] found no significant association between fatigue assessed with the FSS and clinical status at admission,

Table 2 Univariable and multivariable analyses of predictors in the study population with and without fatigue (data are presented as the absolute number of patients with percentages in parentheses with the exception of age, which is listed as mean value ± SD)

Variable[†]	Fatigue Severity Scale (FSS)		Univariable analysis		Multivariable analysis	
	FSS ≥ 4 *n* = 248	FSS < 4 *n* = 108	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age in years at ictus, mean ± SD	55.4 ± 11.4	56.5 ± 14.8	0.993 (0.975–1.011)	0.438		
Sex, male	84 (33.9%)	31 (28.7%)	1.272 (0.777–2.083)	0.338		
Nicotine use at time of ictus						
Never	60 (24.4%)	46 (43.0%)	1.000 (ref.)	0.002		
Former	40 (16.3%)	16 (15.0%)	1.917 (0.956–3.842)	0.067		
Current	146 (54.1%)	45 (42.1%)	2.487 (1.495–4.139)	< 0.001	2.104 (1.305–3.394)[‡]	0.002
Aneurysm location						
ACoA/ACA	109 (44.0%)	39 (36.1%)	1.000 (ref.)	0.369		
MCA/ICA	102 (41.1%)	52 (48.1%)	0.702 (0.428–1.152)	0.161		
Vertebrobasilar	37 (14.9%)	17 (15.7%)	0.779 (0.394–1.538)	0.472		
Endovascular treatment	139 (56.3%)	55 (51.4%)	1.217 (0.772–1.918)	0.398		
Hunt and Hess 4–5	57 (23.0%)	15 (13.9%)	1.850 (0.995–3.441)	0.052		
Glasgow Coma Scale						
GCS 15–14	151 (60.9%)	85 (78.7%)	1.000 (ref.)	0.006	1.000 (ref.)	0.011
GCS 13–9	48 (19.4%)	11 (10.2%)	2.456 (1.211–4.981)	0.013	2.490 (1.206–5.140)	0.014
GCS 8–3	49 (19.8%)	12 (11.1%)	2.299 (1.159–4.560)	0.017	2.128 (1.034–4.381)	0.040
Modified Fisher 3–4	141 (57.1%)	45 (41.7%)	1.862 (1.178–2.944)	0.008	1.403 (0.837–2.350)	0.198
Modified LeRoux 6–16	37 (15.0%)	17 (15.7%)	0.943 (0.505–1.762)	0.854		
Loss of consciousness at ictus	114 (46.2%)	32 (29.6%)	2.036 (1.256–3.299)	0.004	1.196 (0.630–2.272)	0.584
Rebleed before treatment	26 (10.5%)	4 (3.7%)	3.045 (1.036–8.950)	0.043	2.680 (0.872–8.236)	0.085
Severe vasospasm	50 (20.2%)	10 (9.3%)	2.487 (1.210–5.115)	0.013	2.298 (1.095–4.823)	0.028
Acute hydrocephalus	179 (72.2%)	60 (55.6%)	2.075 (1.297–3.322	0.002	1.268 (0.712–2.258)	0.419
Chronic hydrocephalus	65 (26.2%)	18 (16.7%)	1.776 (0.995–3.171)	0.052		
Intracerebral hemorrhage	54 (21.8%)	18 (16.7%)	1.392 (0.772–2.508)	0.271		
New cerebral infarction	73 (29.4%)	24 (22.2%)	1.460 (0.860–2.479)	0.161		

[†] Some variables have missing values (number of missing patients in parentheses): nicotine use at time of ictus (3 missing), treatment modality (2 with spontaneous aneurysm thrombosis are excluded), modified Fisher (1 missing), LeRoux (1 missing), LOCi (1 missing), and severe vasospasm (1 missing). [‡] Nicotine use were dichotomized (never/former versus current)

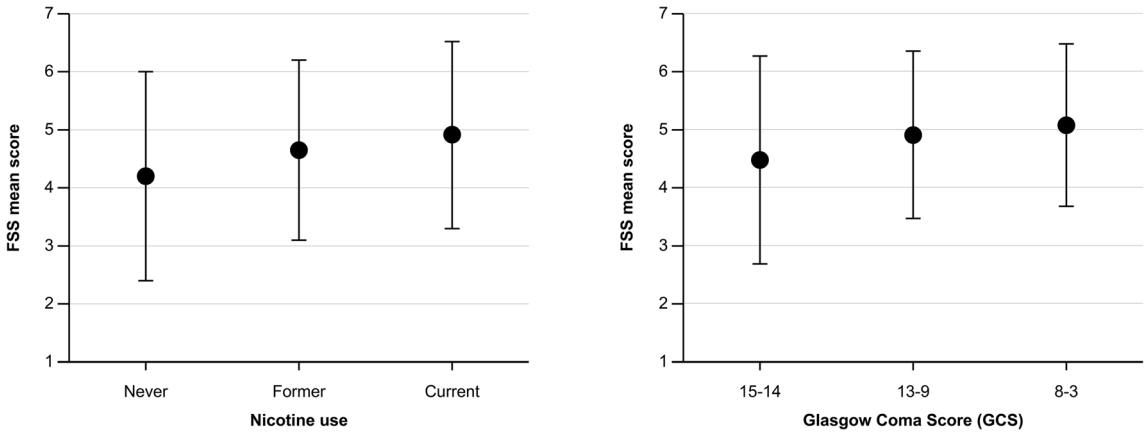

Fig. 3 Mean Fatigue Severity Score (FSS) versus nicotine use (left) and Glasgow Coma Score (right)

aneurysm localization, method of aneurysm repair, rebleed, secondary ischemia, or hydrocephalus. Khajeh et al. [26] found severity of SAH (in terms of World Federation of Neurosurgical Societies) to be associated with fatigue, but all other clinical characteristics (i.e., age, gender, body mass index, hydrocephalus, vasospasm, delayed cerebral ischemia (DCI), intraventricular hemorrhage (IVH), intraparenchymal hemorrhage, and rebleed) were not predictive of persistent fatigue. Buunk et al. [7] found a significant relationship between mental fatigue and external CSF drainage, but not with SAH type. Our results confirm in part their findings of lack of relation between clinical variables and fatigue; however, our univariable regression analysis identified GCS, rebleed, acute hydrocephalus, and large amounts of subarachnoid blood as relevant predictors of fatigue. This may be due to differences in evaluating the various variables or that our study cohort is

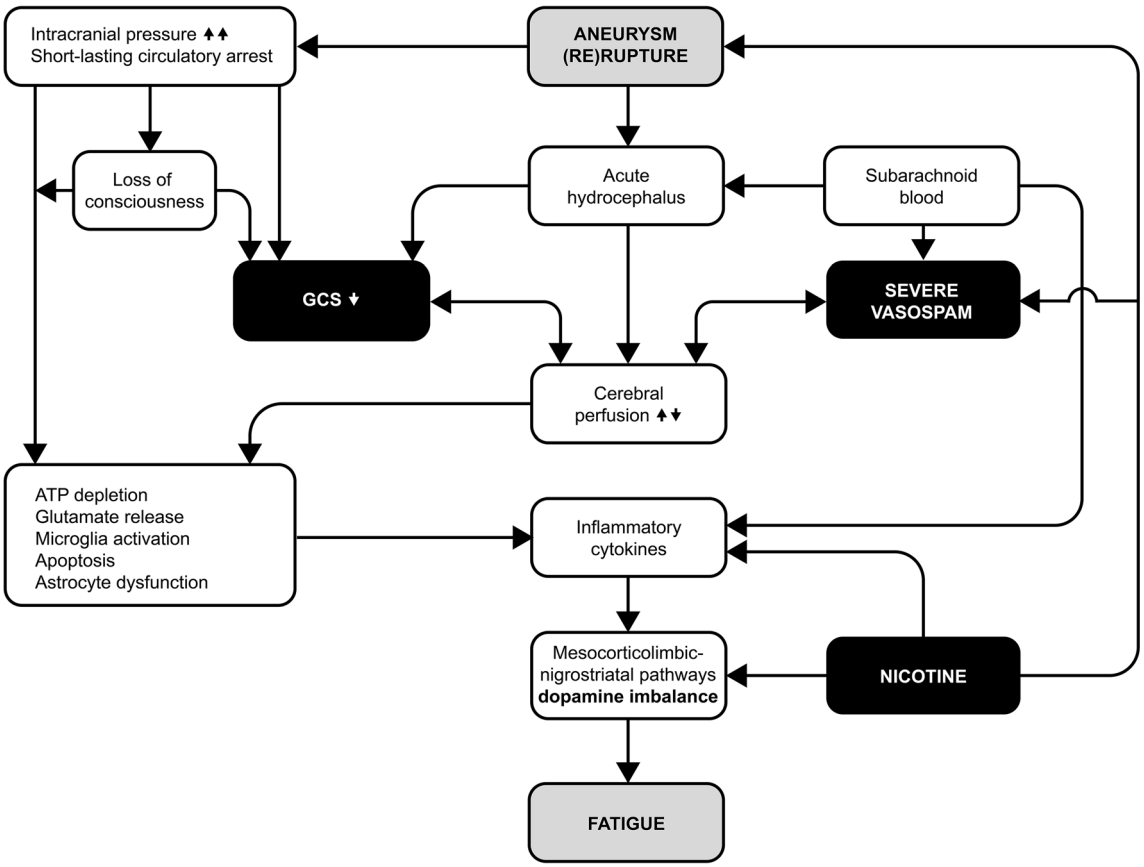

Fig. 4 Relationship of variables of aneurysmal hemorrhage, which culminate in processes attributable to the development of fatigue. Black boxes indicate independent predictors of fatigue in the present study. GCS, Glasgow Coma Score [23]; ATP, adenosine triphosphate

more than three times larger than the patient populations examined in the earlier studies, rendering our results more robust.

Relevant predictors in our study, like LOCi, GCS, large amount of subarachnoid blood, and severe vasospasm, can also be linked to the inflammatory cytokine hypothesis with dopamine imbalance: when an aneurysm ruptures, there is an instant, vast increase in intracranial pressure (ICP), leading to cerebral circulatory arrest of varying length [35]. In some patients, the ICP increase is so brief or so moderate that they do not become unconscious, whereas up to half of aSAH patients experience some form of LOCi [20]. Prolonged LOCi often will lead to the patient being admitted with reduced GCS. If no LOCi occurred, or when awakening from LOCi, acute hydrocephalus can cause an additional and gradual decline in GCS. Presently, acute hydrocephalus was a relevant factor in univariable regression analysis, but did not prove to be an independent predictor like GCS, where we also saw that mean FSS increased the lower GCS was. Even very short-lasting circulatory arrest initiates a cascade of cellular pathophysiologic events as neuronal oxygen stores are depleted within 15–20 s [42]. Prolonged reduced consciousness in the setting of untreated acute aSAH is the result of local parenchymal damage and suboptimal cerebral perfusion pressure (CPP). This results in anaerobic glycolysis in the first 4–5 min and leads to depletion of brain glucose and adenosine triphosphate [33]. Such inflammation and downregulation of astrocytes leading to dysfunctional glutamate transmission have been attributed to mental fatigue after traumatic brain injury [24]. Microglia and endothelial cells become activated, and through complex mechanisms, proinflammatory cytokines (among others tumor necrosis factor-α, IL-6, and IL-8) are released [33].

The most feared complication during the first 2 weeks after aSAH is cerebral vasospasm [22]. Most patients experience some degree of vasospasm in conjunction with their aSAH, whereas usually only severe vasospasm becomes symptomatic due to reduced CPP. Without treatment adjustments to preserve adequate CPP, cerebral ischemia can occur or be aggravated [22]. Large amounts of subarachnoid blood represent a risk factor for developing vasospasm [22]. We found severe vasospasm to be an independent predictor of fatigue and large amount of subarachnoid blood was presently a predictor in the univariable analysis. Vasospasm after aSAH is not a purely mechanical event, but develops over days as an inflammatory response to blood degradation [15] and leads to a thickening of the arterial wall and thereby reduced arterial lumen. The inflammatory cytokines found in vasospasm comprise tumor necrosis factor-α, IL-1α, IL-1β, IL-6, and IL-8 [15], and in severe vasospasm, IL-6 seems to be predominant [22]. Hence, vasospasm is linked to the same inflammatory cytokines that are upregulated in patients with ischemia and/or reduced consciousness. Of these, IL-6 and tumor necrosis factor-α have also been directly related to the development of fatigue [40]. Inhibitors of tumor necrosis factor-α and antibodies against IL-1β have improved fatigue symptoms in patients with psoriasis, diabetes, and rheumatoid arthritis [25]. Substances ameliorating the dopamine imbalance, like methylphenidate or OSU6162, have also been mentioned as potential pharmacological therapies of fatigue [24]. Figure 4 illustrates the complex, interwoven relationship of the presently investigated variables of aSAH, which eventually may culminate in processes attributable to the development of fatigue.

Limitations

This study has several limitations. We used only one measure of fatigue, and there may have been other aspects of fatigue that remained under- or overestimated by the use of the FSS questionnaire. It is also uncertain whether administration of FSS by telephone interview in comparison with standard paper-and-pencil self-administration influenced the patients' response style. We showed the frequency of fatigue to be remarkable stable up to 7 years after ictus, but time trajectories cannot be established with our cross-sectional study design. Although common to many stroke studies, generalizability of our findings was limited by excluding patients living at a nursing home, with pronounced cognitive sequelae or aphasia. This concerned only a small group of survivors (< 15%); however, it might have led to a selection bias where our estimate is an inaccurate reflection of fatigue prevalence in the overall aSAH population. On the other hand, we included patients from the entire range of aSAH severity. Finally, we assessed factors related to clinical status in the acute phase. Several other predictors such as premorbid personality traits (e.g., neuroticism, coping style), psychiatric comorbidity (e.g., mood disorder), and somatic comorbidity (e.g., sleep disorder, hypopituitarism, cancer, rheumatic diseases) were not measured. Future studies should include an even bigger range of possible factors related to fatigue. Altogether, these limitations should be considered when interpreting our findings. Still, our study included a large number of patients and is novel in that it could identify relevant clinical predictors of post-aSAH fatigue.

Conclusions

The prevalence of fatigue in the chronic phase after aSAH was 69.7%. Fatigue remained a common and stable symptom up to 7 years after the ictus. Nicotine use, reduced consciousness with GCS < 14 at admission, and severe vasospasm were independent predictors from the acute phase of aSAH that more than doubled the risk to develop post-aSAH fatigue. Inflammatory cytokines causing dopamine imbalance may be a common denominator for fatigue and the presently identified predictors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Comments

Let us say what is intuitive; in aSAH and all serious neurosurgical diseases that we treat. Sicker patients with more comorbidities have more protracted recovery periods. This is known to all experienced neurosurgeons and is part of our daily lives.

Now here the authors have applied a scientific rationale in a prospective study to further characterize our intuitive observations. The scientific aim was to study many independent factors to see which could contribute to long-term post SAH fatigue on a standard measure. In their paper, univariable analysis identified current nicotine use, loss of consciousness at ictus, rebleed prior to aneurysm repair, reduced consciousness to Glasgow Coma Scale (GCS) < 14, large amounts of subarachnoid blood, the presence of acute hydrocephalus, and severe vasospasm as factors that were significantly associated with fatigue. In multivariable analysis, current nicotine use, reduced GCS, and severe vasospasm were independent predictors that all more than doubled the risk to develop post-aSAH fatigue.

Experienced surgeons would have predicted this. None of these are really variables that we can control. Nonetheless, it is useful to have this data scientifically quantified in a proper study, if only to give us a better foundation for discussions of expectations with patients and family.

Christopher Miranda Loftus
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II

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Fatigue After Aneurysmal Subarachnoid Hemorrhage: Clinical Characteristics and Associated Factors in Patients With Good Outcome

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Fatigue after aneurysmal subarachnoid hemorrhage (post-aSAH fatigue) is a frequent, often long-lasting, but still poorly studied sequel. The aim of the present study was to characterize the nature of post-aSAH fatigue with an itemized analysis of the Fatigue Severity Scale (FSS) and Mental Fatigue Scale (MFS). We further wanted to assess the association of fatigue with other commonly observed problems after aSAH: mood disorders, cognitive problems, health-related quality of life (HRQoL), weight gain, and return to work (RTW). Ninety-six good outcome aSAH patients with fatigue completed questionnaires measuring fatigue, depression, anxiety, and HRQoL. All patients underwent a physical and neurological examination. Cognitive functioning was assessed with a neuropsychological test battery. We also registered prior history of fatigue and mood disorders as well as occupational status and RTW. The patients experienced fatigue as being among their three most disabling symptoms and when characterizing their fatigue they emphasized the questionnaire items "low motivation," "mental fatigue," and "sensitivity to stress." Fatigue due to exercise was their least bothersome aspect of fatigue and weight gain was associated with depressive symptoms rather than the severity of fatigue. Although there was a strong association between fatigue and mood disorders, especially for depression, the overlap was incomplete. Post-aSAH fatigue related to reduced HRQoL. RTW was remarkably low with only 10.3% of patients returning to their previous workload. Fatigue was not related to cognitive functioning or neurological status. Although there was a strong association between fatigue and depression, the incomplete overlap supports the notion of these two being distinct constructs. Moreover, post-aSAH fatigue can exist without significant neurological or cognitive impairments, but is related to reduced HRQoL and contributes to the low rate of RTW.

Keywords: aneurysmal subarachnoid hemorrhage (aSAH), fatigue, mood disorders, cognitive function, health-related quality of life (HRQoL), return to work (RTW)

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease with case fatality rates of 27–44% (Nieuwkamp et al., 2009). Even though the mortality rates are high, survival has improved due to early intervention and advances in management. Remarkably, most aSAH survivors recover without significant neurological deficits, however, even patients with good outcome report substantial problems with fatigue, as well as cognitive and emotional problems (Al-Khindi et al., 2010; Nordenmark et al., 2019a; Nussbaum et al., 2020; Tang et al., 2020). Fatigue represents the most frequent symptom after aSAH and is found in 50–70% of patients even several years after the hemorrhage (Kutlubaev et al., 2012; Western et al., 2020).

There is no consensus concerning a definition of fatigue. Chaudhuri and Behan (2004) have described fatigue as problems with the initiation of or sustaining voluntary activities. They discriminate between peripheral fatigue at the muscular level and fatigue originating in the central nervous system (central fatigue). The latter is characterized as a feeling of constant exhaustion and may have a cognitive component (mental fatigue). Mental fatigue is a prominent symptom in a diversity of neurological diseases (Chaudhuri and Behan, 2004; Yoshii et al., 2006; Penner and Paul, 2017; Arm et al., 2019). Fatigue after aSAH has been less extensively investigated. Buunk et al. (2018) found mental fatigue to prevail in aSAH patients. Levels of fatigue after aSAH were also found to be related to outcome measures like Return to Work (RTW) and Glasgow outcome score extended (GOSE). In the study by Sörbo et al. (2019), a majority (57%) of aSAH patients experienced mental fatigue, however a more precise delineation of the core problems in individuals with post-aSAH fatigue is still lacking.

Not only the definition, but also the quantification of fatigue is challenging, and currently, questionnaires are the only validated tools available to this end (De Doncker et al., 2018). One of the most commonly used questionnaires is the Fatigue Severity Scale (FSS; Krupp et al., 1989) assessing the impact of fatigue on daily life. A relatively new scale, the Mental Fatigue Scale (MFS; Johansson et al., 2010), has been developed for the assessment of mental fatigue and related symptoms and could possibly give more information regarding the mental aspects of fatigue than the FSS. Combining the information collected by the FSS and MFS could hence provide further characterization of the nature of fatigue after aSAH. In clinical experience, many aSAH patients also complain about a long–term weight gain that they cannot explain by nutritional changes. Inactivity may contribute to this weight gain; inactivity possibly caused by fatigue. When presently investigating fatigue, we, therefore, included weight change over time to see if weight gain represents a surrogate marker for the severity of physical fatigue.

In addition to fatigue, mood disorders, and cognitive problems, aSAH survivors commonly experience reduced Health-Related Quality of Life (HRQoL) and a low rate of RTW (Visser-Meily et al., 2009; Passier et al., 2011b; Czapiga et al., 2013; Harris, 2014; Taufique et al., 2016; Buunk et al., 2019). A more precise knowledge of the challenges fatigue poses could facilitate targeted rehabilitation programs. Moreover, it is not clear to which extent fatigue contributes to mood disorders and cognitive problems. In this respect, it is relevant to know if mood disorders are secondary to or amplified by fatigue rather than representing an autonomous entity requiring antidepressant or anxiolytic treatment.

The aim of the present study was to characterize the nature of fatigue after aSAH with an itemized analysis of the FSS and MFS questionnaires. We further wanted to assess if and how fatigue after aSAH associates with other commonly observed problems after aSAH like mood disorders, cognitive problems, reduced HRQoL, weight gain, and RTW. To this end, we investigated 96 patients in the chronic phase after aSAH that all suffered from fatigue and had been included in a clinical trial to investigate the effect of the substance (-)-OSU6162 on fatigue after aSAH.

MATERIALS AND METHODS

Data for the present study were acquired within the randomized clinical trial (RCT) "OSU6162 in the treatment of fatigue and other neuropsychological sequelae after aneurysmal subarachnoid hemorrhage—a double-blind, randomized, placebo-controlled study" (EudraCT no. 2016-004739-19; ClinicalTrials.gov Identifier: NCT03209830). The study was also approved by the regional ethics committee (REC, reference: 2016/2214). The substance (-)-OSU6162 is a stabilizer of the neurotransmitter dopamine and studies have shown that it may have a positive effect on fatigue (Johansson et al., 2012; Kloberg et al., 2014; Haghighi et al., 2018; Nilsson et al., 2018).

Patients

Patients (≥18 years) in the chronic phase (≥1 year) after treatment at our hospital for aSAH between January 2012 and March 2018, and permanently living in the South-Eastern Norway Regional Health Authority were eligible. A clinical neuropsychologist conducted the recruitment by telephone interview. All patients with a mean FSS score ≥4 were invited for assessment at the hospital. We excluded patients unable to conduct the different assessments, handle the instruments used for evaluation, or those who were unable to give consent. We also excluded those that had undergone brain surgery <12 months prior to inclusion, patients with brain tumor, cerebral arteriovenous malformation, inadequately treated hydrocephalus, epilepsy, cerebral paresis, and neurodegenerative disease. Pregnancy also prohibited participation, as did active drug abuse, severe blood test deviations from normal and an electrocardiogram with prolonged QTc time >480 ms.

Due to possible interactions with (-)-OSU6162, we further excluded patients using metabolic enzyme inhibitors and inducers and those using drugs with a narrow therapeutic window or requiring individual dose adjustments. The following Anatomical Therapeutic Chemical (ATC) Classification System categories were not allowed: N06B A+X, N07A, N06A G+X, N05A, N03A, J04A, J01D H, L04A D, B01A A, C01A A, H01B A, and N04B D.

Assessments

Demographic Data/aSAH Characteristics

Age, gender, weight, height, education level, and pre-ictal/current work status was recorded during the baseline visits of the RCT. During the same visits, the patients also underwent a neurological examination and were later scored using the National Institutes of Health Stroke Scale (NIHSS). Weight at ictus was retrieved from the medical journals. Change in body mass index (BMI, kg/m^2) from ictus to baseline assessment in the study was calculated and adjusted for months since the ictus. From the medical journals, we also retrieved the clinical condition according to Hunt and Hess (Hunt and Hess, 1968) just prior to aneurysm repair or prior to intubation in those admitted intubated, aneurysm localization, method of aneurysm repair, and any treatment for acute hydrocephalus (need of external drainage of cerebrospinal fluid) or chronic hydrocephalus (implanted shunt). We noted the acquisition of any radiologically documented new cerebral infarction during the acute phase of aSAH, regardless of cause. Clinical outcome at one year after the ictus was assessed using the modified Rankin Score (Rankin, 1957; van Swieten et al., 1988).

Fatigue

A prior history of fatigue was registered from the medical records at aSAH admission and by asking the patient: "did you experience fatigue before your aSAH" (yes/no). Patients who answered "yes" were encouraged to describe, regardless of cause, the nature of their pre-ictal fatigue. Those who reported pre-ictal fatigue with an intensity and severity that caused problems in their daily lives were defined as having fatigue before the hemorrhage (Lynch et al., 2007).

Post-aSAH fatigue was measured using the Norwegian version of the FSS (Krupp et al., 1989; Lerdal et al., 2005) and the MFS (Johansson et al., 2010). FSS consists of nine items about the impact of fatigue on daily life, where each statement is scored on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The nine items of the FSS questionnaire are: (1) My motivation is lower when I am fatigued; (2) Exercise brings on my fatigue; (3) I am easily fatigued; (4) Fatigue interferes with my physical functioning; (5) Fatigue causes frequent problems for me; (6) My fatigue prevents sustained physical functioning; (7) Fatigue interferes with carrying out certain duties and responsibilities; (8) Fatigue is among my three most disabling symptoms; and (9) Fatigue interferes with my work, family, or social life. The FSS score is the mean of the nine item scores. A mean FSS score of $\geq$4 is considered indicative of fatigue (Krupp et al., 1989). Correspondingly, the MFS questionnaire comprises 15 questions regarding affective, cognitive, and sensory symptoms related to fatigue. The 15 items of the MFS questionnaire are: (1) Fatigue in general; (2) Lack of initiative; (3) Mental fatigue; (4) Mental recovery; (5) Concentration difficulties; (6) Memory problems; (7) Slowness of thinking; (8) Sensitivity to stress; (9) Emotional instability; (10) Irritability; (11) Sensitivity to light; (12) Sensitivity to noise; (13) Decreased sleep; (14) Increased sleep; and (15) 24-h variations. Items 1–14 are scored on a scale ranging from 0 to 3; where 0 corresponds to normal function, 1 indicates a problem, 2 indicates a pronounced problem and 3 a maximal problem. The patient can also choose an answer in between the exemplified alternatives; i.e., 0.5, 1.5, and 2.5. Item 15, which is not included in the total sum score, indicates which time of the day is felt best and worst if there is a diurnal variation. An MFS sum score of $\geq$10.5 is suggestive of mental fatigue (Johansson and Ronnback, 2014).

Mood Disorders

A prior history of depression and anxiety was registered from the medical records at aSAH admission and by asking the patient: "did you experience psychiatric problems before your aSAH" (yes/no). Patients who answered "yes" were encouraged to describe the nature of the symptoms, severity and, duration. Those who reported depressive or anxiety symptoms, often in combination with therapy or pharmacological treatment, interfering with activities of daily life, were defined as having depression or anxiety before the hemorrhage.

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and The Beck Anxiety Inventory (BAI; Beck et al., 1988) were used to assess the frequency and severity of depressive and anxiety symptoms, respectively, during the past 2 weeks. Both scales are 21-items self-report questionnaires with each item rated on a 4-point scale from 0 to 3 with higher scores indicating more severe symptomology. A BDI-II score of $\geq$20 was defined as clinical depression (moderate to severe depressive symptoms) whereas a BAI score of $\geq$16 was defined as clinical anxiety (moderate to severe anxiety symptoms). In this study, mood disorder was defined as the presence of clinical depression and/or clinical anxiety.

Cognitive Function

The following six cognitive domains were examined: sensomotor function, attention, psychomotor speed, verbal learning, verbal memory, and executive function.

All patients underwent a standardized neuropsychological test battery that covered the six cognitive domains mentioned above. We selected tests that are widely used in routine neuropsychological practice and sensitive to deficits after brain injury. All tests were administered in the same order to all patients. The *Sensomotor function* was measured with Grooved Pegboard (Halstead-Reitan Neuropsychological Battery; Heaton et al., 1991) and Trail Making Test condition 5 from Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) whereas *Attention* was assessed using the Trail Making Test condition 1 from D-KEFS, Digit Span from Wechsler Adult Intelligence Scale—fourth edition (WAIS-IV; Wechsler, 2008), and Conners' Continuous Performance—3rd edition (CPT-III; Conners, 2014). *Psychomotor speed* was examined using the Trail Making Test condition 2 and 3 (D-KEFS) and the Color-Word Interference Test condition 1 and 2 (D-KEFS). *Verbal learning* and *Verbal memory* were measured using the California Verbal Learning Test—Second edition (CLVT-II; Delis et al., 2000) while *Executive function* was assessed using the Trail Making Test condition 4 (D-KEFS) and Color-Word Interference Test condition 3 and 4 (D-KEFS).

All tests were scored using published norms and, where available, age-adjusted scores for a normal population. In order to compare the results with a normal population with similar demographic features, scores were converted into *z*-scores. *Z*-scores of patients on all individual tests were stratified into 4 categories: "normal" (*z*-scores > -1.00), "mild impairment" (*z*-scores between -1.00 and -1.49), "moderate impairment" (*z*-scores between -1.50 and -2.00), and "deficit" (*z*-scores <-2.00). Furthermore, the proportions of patients within these four categories were averaged per cognitive domain.

Health-Related Quality of Life

HRQoL was measured using the Short Form Health Survey (SF-36; Ware and Sherbourne, 1992). The SF-36 is a 36-item self-report questionnaire measuring subjective HRQoL in 8 health-related domains: physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. Scores were converted to updated norms based on the Norwegian version of SF-36 (Garratt and Stavem, 2017) and *t*-scores <37 were defined as outside the normal range.

Return to Work

Only patients employed at the time of hemorrhage were included in the RTW analysis. The patients were scored as follows: no RTW (work before but not after aSAH), partial RTW (reduced work after as compared to before aSAH), and full RTW (same amount of work before and after aSAH).

Statistical Analysis

Statistical analysis was performed with IBM SPSS version 25 for Windows (Armonk, NY: IBM Corp). Continuous variables were presented by mean and standard deviation, and independent samples *t*-test was used to compare differences between groups. Continuous variables which were not normally distributed were presented with median and range, and the Mann–Whitney *U* test was used for differences between groups. Categorical variables were presented as frequencies or percentages, and we used the Chi-Square test to compare differences between groups. The itemized analysis was conducted by comparing the mean FSS and mean MFS item scores against the mean FSS score ± 2 SEM and mean MFS item score ± 2 SEM for the whole group ($N = 96$). FSS and MFS item scores defined as prominent features of post-aSAH fatigue also corresponded to results of skewness (i.e., highest negative values). Bivariate and partial Pearson correlation coefficient was used to explore FSS and MFS with continuous variables and adjust for covariates. Statistical significance was set at 0.05 (two-sided).

RESULTS

Patients

A total of 749 patients were admitted for aSAH between January 2012 and March 2018, of whom 677 received active treatment, 430 patients were eligible for a telephone interview, 368 completed prescreening by telephone and 96 patients completed the full assessment at the hospital (see **Figure 1**). The time from hemorrhage to inclusion was median 25 months (range 12–83 months). The characteristics of the 96 included patients are displayed in **Table 1**. Whereas the 96 included and the 272 excluded patients did not differ with respect to gender [$X^2_{(1)} = 0.02$, $p = 0.886$], aneurysm location [$X^2_{(1)} = 0.38$, $p = 0.540$] or mode of aneurysm repair [$X^2_{(1)} = <0.01$, $p = 0.969$], the excluded patients were significantly older at the time of hemorrhage [$t_{(1)} = 3.58$, $p = <0.001$] and in better clinical condition (HH 1–3 vs. HH 4–5) prior to aneurysm repair as compared to the included patients [$X^2_{(1)} = 4.29$, $p = 0.038$].

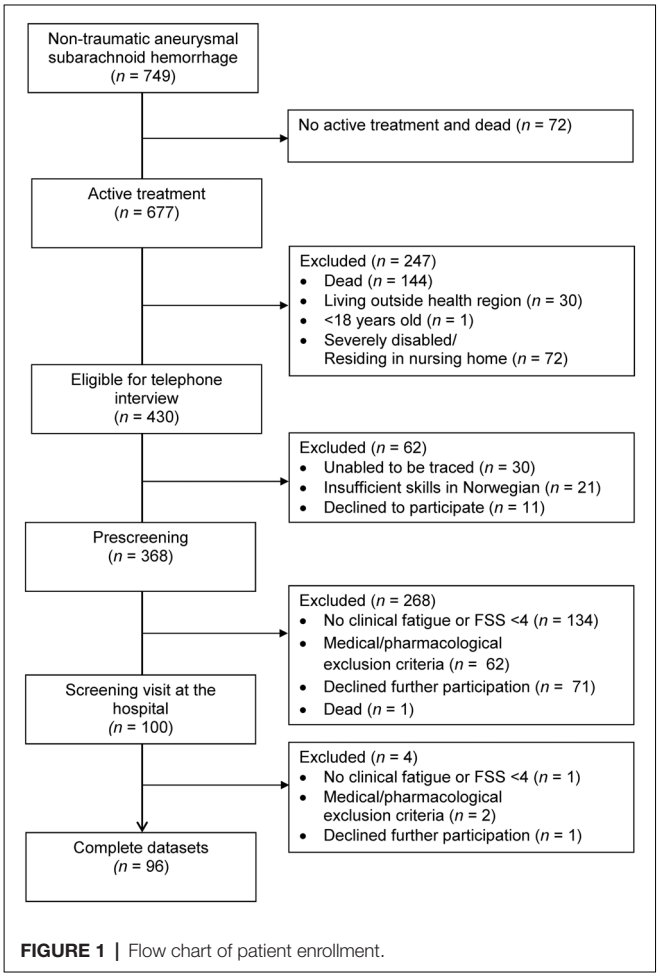

FIGURE 1 | Flow chart of patient enrollment.

Post-aSAH Fatigue

For all 96 patients, the mean FSS score was 6.0 ± 0.8, and the MFS sum score was 18.1 ± 5.6. Scores on the two fatigue measures were closely connected, where higher scores on FSS were significantly related to higher scores on MFS [$r_{(94)} = 0.47$, $p = <0.001$].

Figures 2 and **3** show which of the nine FSS items and the 14 MFS items that stood out as most and less prominent by displaying the mean scores for each item for the entire group and those with mood disorders against the mean FFS score ± 2 SEM and the mean MFS item score ± 2 SEM.

TABLE 1 | Characteristics of patients with post-aSAH fatigue (N = 96).

	n	%
Demographic characteristics		
Age (years) at assessment, median (range)	57 (22–74)	
Sex, female	65	67.7
Body Mass Index (BMI)		
BMI at ictus, mean ± SD (range)	26.8 ± 5.4 (15.8–41.2)	
Education level		
Lower secondary school	13	13.5
Upper econdary school	36	37.5
Undergraduate school	33	34.4
Graduate school	14	14.6
Work status at ictus		
Paid work	78	81.3
Retirement/disability leave	15	15.6
Student	3	3.1
Prior history of fatigue and mood disorders		
Fatigue before aSAH	13	13.5
Depression before aSAH	22	22.9
Anxiety before aSAH	12	12.5
aSAH characteristics		
Time since ictus (months), median (range)	25 (12–83)	
Method of aneurysm repair		
Surgical	43	44.8
Endovascular	53	55.2
Aneurysm localization		
Anterior circulation	83	86.5
Posterior circulation	13	13.5
Hunt and Hess (HH)		
1	25	26.0
2	33	34.4
3	12	12.5
4	16	16.7
5	10	10.4
Acute hydrocephalus	69	71.9
Chronic hydrocephalus	24	25.0
Cerebral infarction*	31	32.3
Characteristics post-aSAH		
Outcome (modified Rankin Score)		
0	5	5.2
1	68	70.8
2	23	24.0
Neurological status at assessment		
NIHHS score, mean ± SD (range)	0.7 ± 1.0 (0–5)	
Body Mass Index (BMI)		
BMI at assessment, mean ± SD (range)	29.3 ± 6.5 (16.5–56.8)	
Monthly change in BMI, mean ± SD (range)	0.1 ± 0.2 (−0.7–0.8)	

*Data are presented as the absolute number of patients with percentages in parentheses with the exception of BMI and NIHHS score, which is listed as mean ± standard deviation and range. Age and time since ictus is reported as median and range. *All new cerebral infarction registered independent of cause (i.e., primary or secondary).*

On the FSS questionnaire (**Figure 2**), the two items that were scored highest by the entire group was "My motivation is lower when I am fatigued" (item 1: 6.5 ± 1.0) and "Fatigue is among my three most disabling symptoms" (item 8: 6.6 ± 0.7). The items "Exercise brings on my fatigue" (item 2: 4.7 ± 2.0) and "Fatigue causes frequent problems for me" (item 5: 5.6 ± 1.4) had the lowest scores; however, within these two items we found the largest differences between all patients and the subgroup with mood disorders. Item 3 "I am easily fatigued" fell just below the ± 2SEM of mean FSS for the entire group, but scored within this range in those with mood disorders. All other items on FFS were above or within the range of cut-off (± 2 SEM).

On the MFS questionnaire (**Figure 3**), the items "Mental fatigue" (item 3: 1.9 ± 0.5) and "Sensitivity to stress" (item 8: 1.9 ± 0.9) stood out with the highest scores. Item 11 "sensitivity to light" (0.9 ± 0.7) and item 13 "decreased sleep" (0.8 ± 0.8) scored lowest. Item 6 "Memory problems", item 9 "Emotional instability", and item 10 "Irritability" scored below the range of cut-off (± 2 SEM) for all 96 patients but scored within or above the range of cut-off in the subgroup of patients with mood disorders. All other items on MFS were above or within the range of cut-off (± 2 SEM).

Fatigue and Mood Disorders

The proportion of patients within the different standardized categories for BDI-II and BAI are listed in **Table 2**. Clinical depression and clinical anxiety were reported by 34.4% and 18.8%, respectively.

There was a positive correlation between mean FSS scores and depressive symptoms (BDI-II) scores with and without adjustment for anxiety symptoms (BAI) score [$r_{(94)}$ = 0.42, p = <0.001; $r_{adj.(93)}$ = 0.34, p = <0.001]. In contrast, the relationship between mean FSS scores and anxiety symptoms (BAI) scores disappeared when adjusted for depressive symptoms (BDI-II) [$r_{(94)}$ = 0.27, p = 0.007; $r_{adj.(93)}$ =−0.02, p = 0.833]. A positive correlation was found between MFS sum scores and depressive symptoms (BDI-II) scores, also when adjusted for anxiety [$r_{(94)}$ = 0.52, p = <0.001; $r_{adj.(93)}$ = 0.30, p = 0.003]. Although still reaching significance, the correlation between MFS sum scores and anxiety symptoms (BAI) was weakened when adjusted for depressive symptoms (BDI-II) [$r_{(94)}$ = 0.49, p = <0.001; $r_{adj.(93)}$ = 0.21, p = 0.043].

Symptoms of depression and anxiety (BDI-II and BAI scores) within demographics, prior history, and aSAH characteristics are presented in **Table 3**. Patients with prior history of depression had both higher BDI-II scores (depressive symptoms) and higher BAI scores (anxiety symptoms) than those without a prior history of depression. In contrast, patients with prior history of anxiety had higher BAI scores (anxiety symptoms), but not higher BDI-II scores (depressive symptoms) than those with no prior history of anxiety. Except for a trend towards higher BDI-II scores (depressive symptoms) among patients with endovascular as opposed to surgical aneurysm repair (17.8 + 8.6 vs. 14.4 + 8.7, p = 0.058), demographical data and aSAH characteristics were not related to BDI-II and BAI scores. Mood disorders (depression and anxiety) were more common in patients undergoing endovascular than surgical aneurysm repair [47.2% vs. 23.3%, p = 0.019].

Fatigue and Demographic Data/aSAH Characteristics

Fatigue scores vs. demographics, prior history, and aSAH characteristics are presented in **Table 4**. Patients with

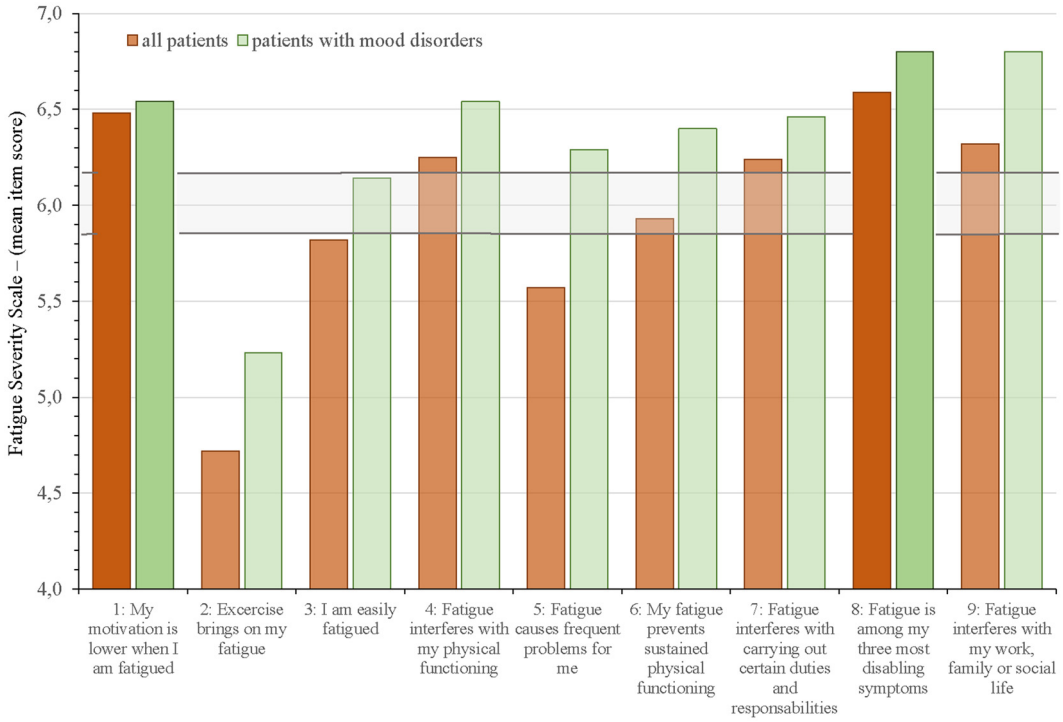

FIGURE 2 | Mean Fatigue Severity Scale (FSS) item scores for all aSAH patients and allocation into subgroup of patients with mood disorders against the mean FSS score ± 2 SEM (horizontal lines). The two FFS items with the highest mean scores are highlighted.

low/intermediate education level had higher mean FSS scores than those with high education level (6.3 ± 0.7 vs. 5.7 ± 0.8, $p = 0.001$) and patients with endovascular aneurysm repair had higher mean FSS scores than those with surgical aneurysm repair (6.2 ± 0.7 vs. 5.7 ± 0.8, $p = 0.002$). There were no significant relationships between MFS sum scores and any of the background variables.

There was no significant relationship between fatigue and neurological impairment as scored with NIHSS [FSS: $r_{(94)} = 0.06$, $p = 0.583$; MFS: $r_{(94)} = 0.17$, $p = 0.094$]. There was also no significant relationship between fatigue and clinical outcome as scored with mRS [FSS: $r_{(94)} = -0.06$, $p = 0.578$; MFS: $r_{(94)} = 0.17$, $p = 0.093$] where all mRS 0 patients [$n = 5$] scored ≥4 on FSS and 60.0% [$n = 3$] scored ≥10.5 on MFS.

Weight gain was significantly associated with mean FSS scores [$r_{(94)} = 0.25$, $p = 0.016$], but not with MFS sum scores [$r_{(94)} = -0.16$, $p = 0.128$]. Further, weight gain was associated with depressive symptoms (BDI-II) [$r_{(94)} = 0.27$, $p = 0.009$], but did not relate to anxiety symptoms (BAI) [$r_{(94)} = 0.06$, $p = 0.572$]. When adjusted for depressive symptoms, mean FSS scores was no longer associated with weight gain [$r_{adj.(93)} = 0.15$, $p = 0.140$].

Fatigue and Cognitive Function

The neuropsychological test performances of the 96 patients are shown in **Figure 4** (see also **Supplementary Material**: Neuropsychological test performance). As illustrated, the percentages of deficits were low and ranged from 3.9% to 8.7% within the six cognitive domains. The highest percentages of deficits were found for the domains "sensomotor function" [8.7%], "verbal memory" [7.6%], and "executive function" [6.9%].

Digit Span Forward (WAIS-IV) was negatively correlated to mean FSS scores [$r_{(94)} = -0.21$, $p = 0.040$, corrected: $p = 0.960$] and CVLT-II recognition Hits was negatively correlated with MFS sum scores [$r_{(94)} = -0.22$, $p = 0.030$, corrected: $p = 0.720$]. These associations were still significant when adjusted for mood disorders [$r_{adj.(93)} = -0.25$, $p = 0.013$, corrected: $p = 0.312$; $r_{adj.(93)} = -0.26$, $p = 0.011$, corrected: $p = 0.264$, respectively]. Grooved Pegboard dominant was negatively correlated with MFS sum scores [$r_{(94)} = -0.20$, $p = 0.046$, corrected: $p = 1.0$], but not when adjusted for mood disorders [$r_{adj.(93)} = -0.19$, $p = 0.062$]. However, none of the correlations remained statistically significant after Bonferroni correction. Hence, both fatigue scores were unrelated to the 24 neuropsychological test performance scores.

Fatigue and Health-Related Quality of Life

Table 2 presents the results for the SF-36 subscales. Approximately half of the patients scored low (experienced problems) on the subscales role-physical, vitality, and social functioning.

We found significant negative correlations between both mean FSS and MFS sum scores and all SF-36 subscales; i.e., more fatigue correlated with poorer HRQoL (lower scores).

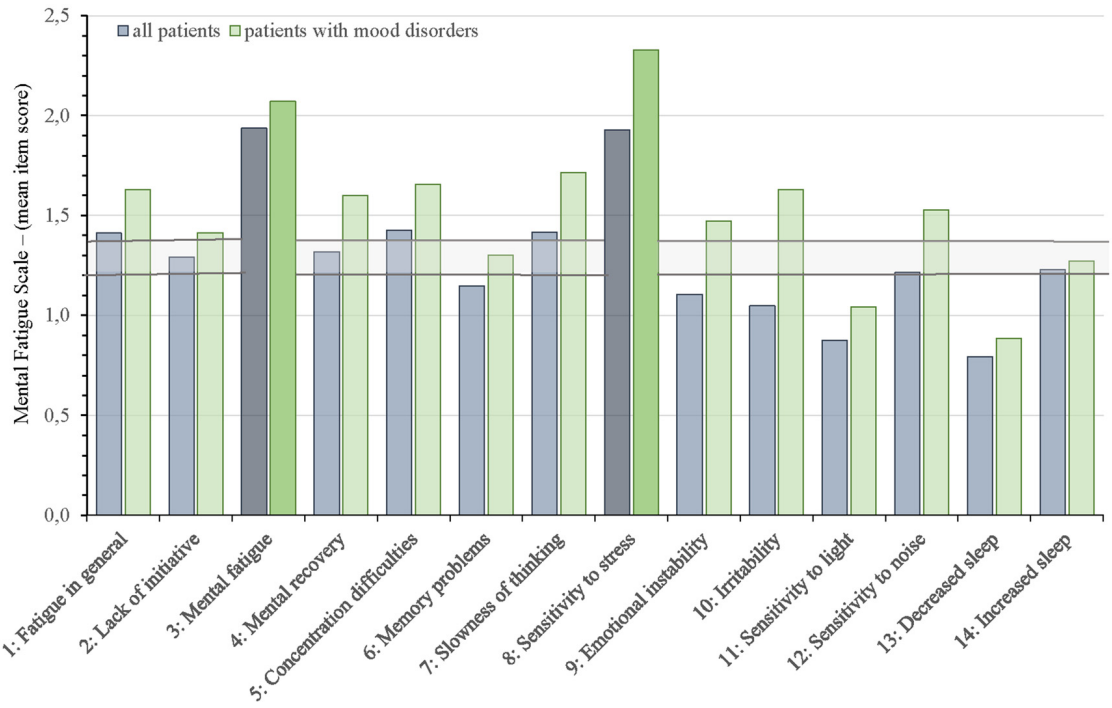

FIGURE 3 | Mean Mental Fatigue Scale (MFS) item scores for all aSAH patients and allocation into subgroup of patients with mood disorders against the mean MFS item score ± 2 SEM (horizontal lines). The two MFS items with the highest mean scores are highlighted.

TABLE 2 | Mean score and percentage of patients with responses in the clinical range on self-assessment questionnaires.

		n	*M*	Range	% in clinical range*
Fatigue					
Fatigue Severity Scale (FSS), mean score		96	6.0 ± 0.8	3.8–7.0	99.0
Mental Fatigue Scale (MFS), sum score		96	18.1 ± 5.6	5.0–41.0	93.8
Depressive symptoms					
Beck Depression Inventory-II (BDI-II), score		96	16.2 ± 8.8	1–45	34.4
	Minimal (0–13)	42			43.8
	Mild (14–19)	21			21.9
Clinical depression	Moderate (20–28)	22			22.9
	Severe (29–63)	11			11.5
Anxiety symptoms					
Beck Anxiety Inventory (BAI), score		96	8.9 ± 7.1	0–29	18.8
	Minimal (0–7)	50			52.1
	Mild (8–15)	28			29.2
Clinical anxiety	Moderate (16–25)	15			15.6
	Severe (26–63)	3			3.1
Health-Related Quality of Life (HRQoL)					
Short Form Health Survey (SF-36), *t*-score					
Physical functioning		96	43.1 ± 10.8	6.0–58.5	26.0
Role-physical		96	39.8 ± 10.0	22.9–62.2	50.0
Bodily pain		96	45.1 ± 10.5	21.7–63.1	19.8
General health		96	40.5 ± 5.8	25.1–54.1	25.0
Vitality		96	35.9 ± 9.0	17.2–55.3	46.9
Social functioning		96	36.3 ± 9.3	8.0–49.2	47.9
Role-emotional		96	43.3 ± 13.7	14.2–59.0	33.3
Mental health		96	43.0 ± 12.8	13.9–64.3	29.2

**Cut-off values for clinical relevance as follows: FSS ≥4; MFS ≥10.5; BDI-II ≥20; BAI ≥16; SF-36 t-score <37.*

All correlations reached $p = \leq 0.001$ significance level except for the associations between fatigue scores and General health subscale which reached a $p = <0.05$ significance level [FSS: $r_{(94)} = -0.32$, $p = 0.002$; MFS: $r_{(94)} = -0.20$, $p = 0.044$]. After adjusting for mood disorders, mean FSS and MFS sum scores were still negatively correlated with all SF-36 subscales [$p = <0.05$] except

TABLE 3 | Relationship between symptoms of depression and anxiety (BDI-II and BAI scores), demographics, prior history of fatigue and mood disorders, and hemorrhage characteristics.

	n	BDI-II score (M)	$t_{(95\% CI)}$	*p*	BAI score (M)	$t_{(95\% CI)}$	*p*
Demographic data							
Age							
≤57 (median)	45	15.8 ± 7.8	−0.449 (−4.380–2.765)	0.654	9.1 ± 6.6	0.291 (−2.458–3.303)	0.772
>57	51	16.6 ± 9.6			8.7 ± 7.5		
Sex							
Female	65	15.6 ± 8.4	−1.070 (−5.837–1.750)	0.288	8.8 ± 7.2	−0.129 (−3.275–2.785)	0.898
Male	31	17.6 ± 9.4			9.0 ± 6.9		
Education level							
Medium	49	17.2 ± 9.5	1.138 (−1.513–5.579)	0.258	9.7 ± 8.3	1.247 (−1.058–4.612)	0.216
High	47	15.2 ± 7.9			8.0 ± 5.5		
Prior history							
Fatigue before aSAH							
No	83	15.7 ± 8.5	−1.509 (−9.070–1.237)	0.135	8.5 ± 7.0	−1.391 (−7.075–1.245)	0.167
Yes	13	19.6 ± 9.8			11.4 ± 7.1		
Depression before aSAH							
No	74	14.7 ± 8.2	−3.192 (−10.517–2.451)	0.002	7.2 ± 6.6	−4.625 (−10.281–4.105)	≤0.001
Yes	22	21.2 ± 9.1			14.4 ± 5.7		
Anxiety before aSAH							
No	85	15.8 ± 8.6	−1.265 (−9.096–2.016)	0.209	8.1 ± 6.7	−3.001 (−10.831–2.206)	0.003
Yes	11	19.4 ± 9.9			14.6 ± 7.6		
aSAH characteristics							
Hunt and Hess (HH)							
Good grade, HH 1–3	70	16.0 ± 9.2	−0.497 (−5.015–3.006)	0.620	9.0 ± 7.6	0.467 (−2.162–3.479)	0.642
Poor grade, HH 4–5	26	17.0 ± 7.6			8.4 ± 5.5		
Aneurysm localization							
Anterior circulation	83	16.8 ± 9.0	1.578 (−1.057–9.239)	0.118	9.2 ± 7.1	1.282 (−1.476–6.857)	0.203
Posterior circulation	13	12.7 ± 6.1			6.5 ± 6.9		
Aneurysm repair							
Surgery	43	14.4 ± 8.7	−1.921 (−6.926–0.115)	0.058	8.4 ± 7.4	−0.556 (−3.695–2.079)	0.580
Coiling	53	17.8 ± 8.6			9.2 ± 6.8		
Acute Hydrocephalus							
No	27	15.7 ± 8.9	−0.392 (−4.749–3.184)	0.696	10.3 ± 7.9	1.280 (−1.127–5.214)	0.204
Yes	69	16.5 ± 8.8			8.3 ± 6.7		
Chronic hydrocephalus							
No	72	17.0 ± 9.2	1.420 (−1.161–6.995)	0.159	9.6 ± 7.3	1.677 (−0.508–6.036)	0.097
Yes	24	14.0 ± 7.2			6.8 ± 5.8		
Cerebral Infarction							
No	65	16.5 ± 9.5	0.474 (−2.902–4.722)	0.637	9.4 ± 7.6	1.119 (−1.218–4.343)	0.267
Yes	31	15.6 ± 7.2			7.8 ± 5.7		

Independent samples t-tests comparisons between groups. Higher BDI-II and BAI scores indicate more symptoms of depression and anxiety, respectively.

for the association between MFS sum scores and General health subscale [$r_{adj.(93)} = -0.07$, $p = 0.483$].

Fatigue and Return to Work

Among the 78 patients that were employed at the time of hemorrhage; 43 [55.1%] had not returned to work (no RTW), 27 [34.6%] had partial RTW, and eight [10.3%] had full RTW. There was a significant difference between the mean FSS score for the different RTW categories ($F_{(2,75)} = 4.17$, $p = 0.019$, **Figure 5A**). The mean FSS score was significantly lower in patients with full RTW [5.40 ± 0.60] as compared to no RTW [6.17 ± 0.69, $p = 0.005$], but not when compared to partial RTW [5.84 ± 0.87, $p = 0.085$]. No significant difference in mean FSS score was seen between partial RTW and no RTW [$p = 0.196$]. **Figure 5B** shows the MFS sum score for the three RTW categories, which were not significantly different [$F_{(2,75)} = 1.50$, $p = 0.231$]. There was further no significant difference in depressive symptoms (BDI-II) scores [$F_{(2,75)} = 1.65$, $p = 0.199$] or anxiety symptoms (BAI) scores [$F_{(2,75)} = 2.93$, $p = 0.060$] for the different RTW categories.

DISCUSSION

Our patients experienced fatigue as being among their three most disabling symptoms and when characterizing their fatigue they emphasized the questionnaire items "low motivation," "mental fatigue," and "sensitivity to stress". Fatigue due to exercise was the least bothersome aspect of fatigue and weight gain was associated with depressive symptoms rather than the severity of fatigue. Although there was a strong association between fatigue and mood disorders, especially for depression, the overlap was incomplete. Post-aSAH fatigue

TABLE 4 | Relationship between mean Fatigue Severity Scale (FSS) scores, Mental Fatigue Scale (MFS) sum scores, demographics, prior history of fatigue and mood disorders, and hemorrhage characteristics.

	n	Mean FSS score (*M*)	*t* (95% CI)	*p*	MFS sum score (*M*)	*t* (95% CI)	*p*
Demographic data							
Age							
≤57 (median)	45	5.9 ± 0.7	−0.626 (−0.421–0.219)	0.533	18.5 ± 5.8	0.526 (−1.673–2.878)	0.600
>57	51	6.0 ± 0.8			17.9 ± 5.4		
Sex							
Female	65	5.9 ± 0.8	−0.902 (−0.496–0.186)	0.370	18.5 ± 5.5	0.828 (−1.413–3.433)	0.410
Male	31	6.1 ± 0.7			17.5 ± 5.7		
Education level							
Low/Intermediate	49	6.3 ± 0.7	3.393 (0.214–0.819)	0.001	18.9 ± 6.3	1.354 (−0.716–3.789)	0.176
High	47	5.7 ± 0.8			17.4 ± 4.6		
Prior history							
Fatigue before aSAH							
No	83	6.0 ± 0.8	−0.502 (−0.586–0.349)	0.617	18.2 ± 5.6	0.333 (−2.764–3.878)	0.740
Yes	13	6.1 ± 0.9			17.7 ± 5.8		
Depression before aSAH							
No	74	5.9 ± 0.8	−1.436 (−0.650–0.104)	0.154	17.6 ± 5.7	−1.760 (−5.022–0.302)	0.082
Yes	22	6.2 ± 0.8			20.0 ± 4.7		
Anxiety before aSAH							
No	85	6.0 ± 0.8	−1.171 (−0.794–0.205)	0.245	17.9 ± 5.5	−1.093 (−5.499–1.595)	0.277
Yes	11	6.3 ± 0.6			19.9 ± 6.5		
aSAH characteristics							
Hunt and Hess (HH)							
Good grade, HH 1–3	70	6.0 ± 0.8	0.359 (−0.295–0.425)	0.721	17.9 ± 5.3	−0.573 (−3.291–1.817)	0.568
Poor grade, HH 4–5	26	5.9 ± 0.9			18.7 ± 6.4		
Aneurysm localization							
Anterior circulation	83	6.0 ± 0.8	−0.713 (−0.634–0.299)	0.478	18.1 ± 4.9	−0.183 (−5.964–5.032)	0.858
Posterior circulation	13	6.1 ± 0.7			18.5 ± 9.0		
Aneurysm repair							
Surgery	43	5.7 ± 0.8	−3.218 (−0.801–0.190)	0.002	17.6 ± 5.6	−0.856 (−3.260–1.295)	0.394
Coiling	53	6.2 ± 0.7			18.6 ± 5.6		
Acute hydrocephalus							
No	27	5.9 ± 0.9	−0.448 (−0.436–0.276)	0.655	19.1 ± 5.2	1.031 (−1.209–3.821)	0.305
Yes	69	6.0 ± 0.8			17.8 ± 5.7		
Chronic hydrocephalus							
No	72	6.0 ± 0.8	1.041 (−0.175–0.561)	0.300	18.3 ± 5.3	0.452 (−2.026–3.220)	0.652
Yes	24	5.9 ± 0.8			17.7 ± 6.6		
Cerebral infarction							
No	65	6.0 ± 0.8	0.761 (−0.211–0.472)	0.448	18.6 ± 5.3	1.045 (−1.146–3.690)	0.299
Yes	31	5.9 ± 0.8			17.3 ± 6.2		

Independent samples t-tests comparisons between groups. Higher FSS and MFS scores indicate higher severity and/or intensity of fatigue.

related to reduced HRQoL, and contributed to low rates of RTW.

Post-aSAH Fatigue

Our itemized analysis favored high scores for questionnaire items that mostly are linked to a mental type of fatigue, whereas those linked to physical activity scored relatively low. Patients reported a disproportionately large drainage of mental energy after executing cognitive tasks or after engaging in a conversation with several people (MFS item 3). Motivation levels were low when fatigued (FSS item 1) and there was a reduced ability to cope with stress and manage tasks under time pressure (MFS item 8). These are typical features of mental fatigue, described as a dynamic process with fluctuation of mental energy levels. Buunk et al. (2018) found a frequency of mental fatigue of 48.4% and of physical fatigue of 38.5% in patients with aneurysmal and non-aneurysmal SAH, which indicates a stronger component of physical fatigue than our results suggest. The instrument used for measuring fatigue was, however, different as Buunk et al. (2018) used The Dutch Multifactor Fatigue Scale. Sörbo et al. (2019) investigated post-aSAH fatigue with the MFS questionnaire only and found 57% of patients scoring ≥10.5 points. They used no other questionnaires and their evaluation of physical fatigue was hence not beyond the means of the present study.

A relationship between pre- and post-stroke fatigue has been reported both in the acute (Lerdal et al., 2011) and chronic phase (Choi-Kwon et al., 2005; Lerdal et al., 2012). We did not find a significant difference between scores of fatigue in patients with or without a prior history of fatigue. To the best of our knowledge,

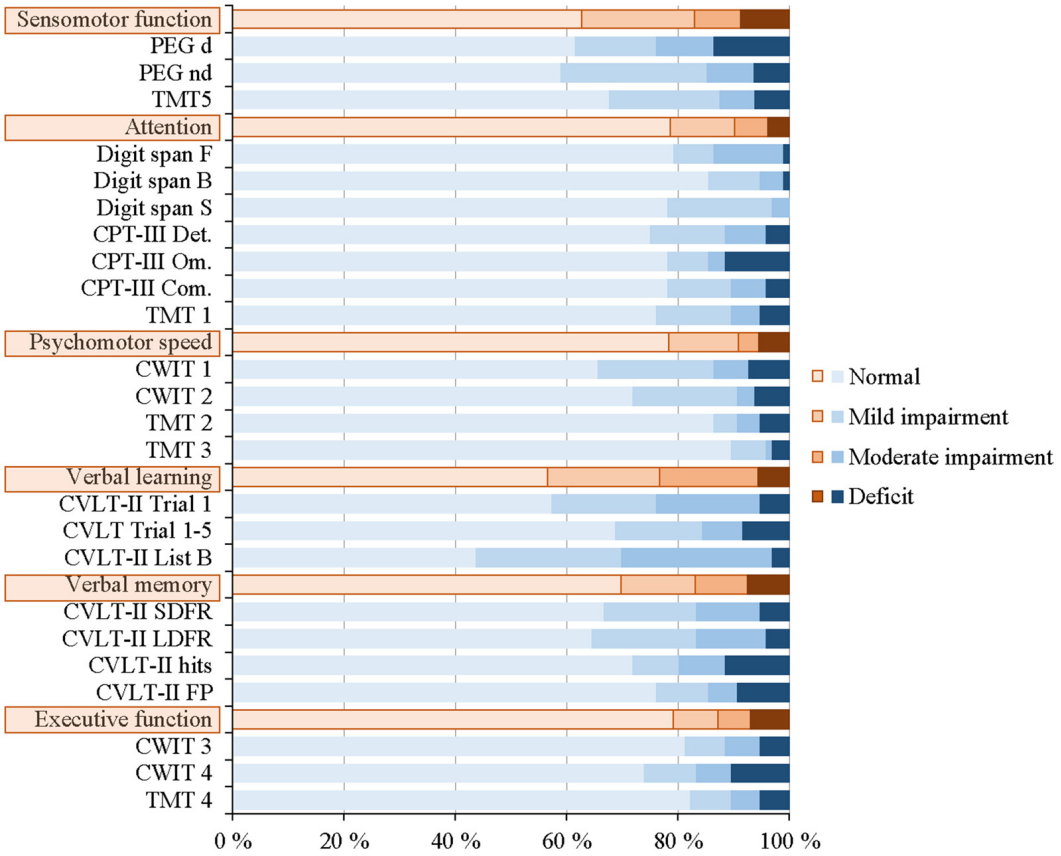

FIGURE 4 | Distribution of normal, mild and moderate impairment, and deficit for the individual neuropsychological tests and the six cognitive domains for all 96 patients.

no data regarding the relationship of pre- and-post-aSAH fatigue have previously been published. We interpret this result, in line with the other findings in the present study, to further support the notion that post-aSAH fatigue is primarily a result of pathological mechanisms caused by the hemorrhage itself.

Fatigue and Mood Disorders

Although the prevalence of mood disorders after aSAH is high (Al-Khindi et al., 2010; Rinkel and Algra, 2011; Vetkas et al., 2013; Tang et al., 2020), few studies have examined the relationship between mood disorders and post-aSAH fatigue. Passier et al. (2011a) found higher fatigue scores 1 year after the ictus in patients scoring high on anxiety and depression than in those without such complaints 3 months after aSAH. Our results are in line with this; i.e., post-aSAH fatigue was strongly associated with depression. Furthermore, post-aSAH fatigue was to some degree associated with anxiety, but to a lesser extent than depression.

Even though post-aSAH fatigue and mood disorders were strongly associated, the overlap was incomplete since a majority of our patients did not have clinical depression or anxiety (65.6% and 81.2%, respectively). Stroke studies have demonstrated that fatigue may occur in the absence of depression (Ingles et al., 1999; van der Werf et al., 2001; Choi-Kwon et al., 2005). Our results suggest that this is also the case for fatigue and mood disorders after aSAH. Fatigue and mood disorders can exist independently, supporting the more commonly accepted notion that these two are distinct entities. Our itemized analysis of the fatigue questionnaires adds to the existing literature that the profile of fatigue characteristics is reported differently in those with post-aSAH fatigue and those with mood disorders. This latter subgroup reported more often that exercise brings on fatigue (FSS item 2), that fatigue causes frequent problems (FSS item 5), and that fatigue causes frequently problems with work, family, and social life (FSS item 9). Furthermore, those with mood disorders reported higher scores for sensitivity to stress (MFS item 8), emotional instability (MFS item 9), irritability (MFS item 10), and sensitivity to noise (MFS item 12). This subgroup may therefore need special attention during rehabilitation.

The temporal relationship between fatigue and mood disorders is not well understood. It is uncertain whether mood disorders after hemorrhage are influenced by personal factors, the aSAH itself, or by its consequences. We found no relationship between mood disorders and aSAH characteristics, which might suggest that mood disorders after aSAH are less likely to be a

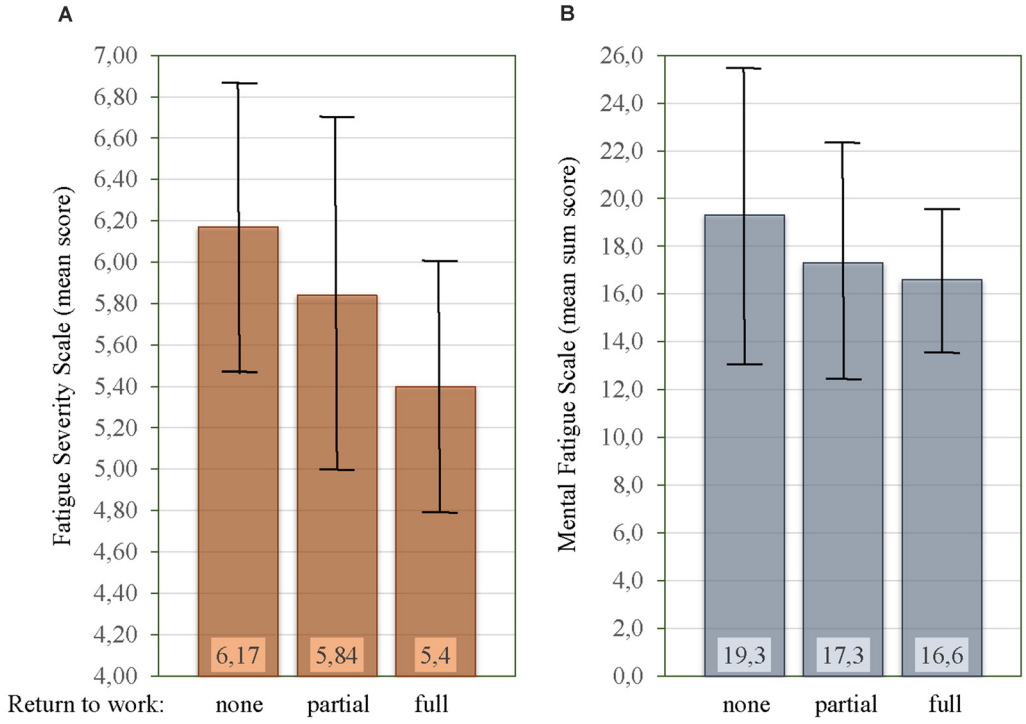

FIGURE 5 | Relationship between mean Fatigue Severity Scale (FSS) score **(A)**, mean Mental Fatigue Scale (MFS) sum score **(B)**, and rate of return to work. Vertical bars on the histogram indicate ± 1 standard deviation.

consequence of direct organic brain injury. However, patients with prior history of mood disorders, and especially depression, had higher scores on BDI-II and BAI than patients without this prior history. A suboptimal coping style could possibly serve as a predisposition for mood disturbance after aSAH (Noble et al., 2008) and therefore indirectly be related to post-aSAH fatigue.

Fatigue and Demographic Data/aSAH Characteristics

Previous studies have failed to show significant relationships between post-aSAH fatigue and age, gender, education level, aneurysm localization, and treatment modality (Passier et al., 2011a; Western et al., 2020). We presently found higher mean FSS scores but similar MFS sum scores among those with low/intermediate as compared to high education level. Selection bias might be of importance as our aSAH population was on average highly educated, whereas the population in Passier et al. (2011a) had primarily low education. The higher mean FSS scores in our patients with endovascular aneurysm repair could be due to the larger fraction of patients with mood disorders in that group.

Sörbo et al. (2019) demonstrated a correlation between MFS score and functional outcome after aSAH as expressed with GOSE, where none of their fully recovered patients (GOSE 8) had an MFS sum score suggestive of mental fatigue (≥10.5). Presently, all five mRS 0 patients scored ≥4 on FSS and three of them scored ≥10.5 on MFS. The mRS may be less sensitive to certain functional impairments as compared to the GOSE. The mRS was presently scored by the clinician during the control visit. A score of mRS 0 may indicate that significant fatigue may be overlooked in a regular interview, especially in patients that have no neurological impairments. Due to the exclusion criteria of our study, we included patients that had very few neurological impairments, and hence one would not expect to find a clear relation between neurological status and fatigue.

Depressed individuals are at higher risk for developing obesity than non-depressed individuals (Blaine, 2008). This can explain that weight gain in our aSAH patients was related to depressive symptoms and not to fatigue. Weight gain was hence no surrogate marker for physical fatigue. Even though FSS item 2 "Exercise brings on my fatigue" was scored higher in those with mood disorders, it was the least prominent FSS item also in that subgroup.

Fatigue and Cognitive Function

Numerous studies have documented cognitive sequelae after aSAH (Al-Khindi et al., 2010; Rinkel and Algra, 2011; Nordenmark et al., 2019b; Burke et al., 2020; Nussbaum et al., 2020). Despite increasing interest in using neuropsychological tests in fatigue research, a lack of correlation between fatigue and neuropsychological performance has been observed across a wide variety of clinical samples (DeLuca, 2005). This concurs with the present findings where few of our patients had cognitive deficits

despite all of them suffering from fatigue. According to DeLuca (2005), the most consistent finding is for subjective fatigue to be more closely related to depression than with objective cognitive performance. This is also in line with our results.

Passier et al. (2011a) demonstrated that aSAH patients with cognitive impairments reported a higher level of fatigue than those without cognitive impairment. In their subgroup of patients with neither physical nor cognitive impairment, however, passive coping style and emotional problems were considered important predictors of fatigue. This could possibly also be so in the present study as our patient cohort of 96 patients closely resembled their subgroup of patients without physical and cognitive deficits. Assessment of coping style among our patients could hence have provided valuable information regarding fatigue.

Fatigue and HRQoL/RTW

It is well-documented that reduced HRQoL is a common sequel after aSAH (Visser-Meily et al., 2009; Al-Khindi et al., 2010; Rinkel and Algra, 2011; Wong et al., 2011; Czapiga et al., 2013; Passier et al., 2013; Taufique et al., 2016). Visser-Meily et al. (2009) found post-aSAH fatigue to be strongly related to a decreased HRQoL. Our findings, where both high mean FSS scores and MFS sum scores were strongly associated with abnormal findings in all subscales of SF-36, concur with that. Even after adjusting for mood disorders, known to be related to reduced HRQoL (Visser-Meily et al., 2009), most of the subscales on SF-36 presently correlated with the post-aSAH fatigue scores.

Limitation in physical and social activities and low vitality were presently reported as the most reduced aspects of HRQoL. Despite their good neurological function, half of our patients still reported physical limitation as the most affected impairment. This was mainly due to their fatigue and not because they actually were physically impaired. Czapiga et al. (2013) also found this subscale to be most impaired in an aSAH population so that this could possibly reflect a physical component of fatigue. A limitation of social activities was also reported as one of the most affected aspects of quality of life. Drainage of mental energy and stress hyper-sensitivity poses a challenge for engagement in social activities. Social withdrawal may therefore be interpreted as a coping mechanism to reduce fatigue.

Despite high functional independence and low frequency of cognitive deficits, we found higher mean FSS scores to be related to a lower rate of RTW. This may be due to a partial overlap in measurement as FSS quantifies the impact of fatigue on daily life. Measuring fatigue with the MFS could not reproduce that clear relationship to RTW, but may perhaps have done so in a larger sample. Mood disorders could not explain our low rate of 10.3% of RTW. Several studies have reported that aSAH survivors have a surprisingly low rate of RTW although being physically capable of working (Hop et al., 2001; Wermer et al., 2007; Passier et al., 2011b; Wallmark et al., 2016; Nordenmark et al., 2019a). Even though the low rate of RTW after aSAH probably is a multifactorial problem, our study demonstrates that fatigue is an important factor to consider when planning occupational therapy. The consequence of the low rate of RTW is not only of economical and psychosocial importance for the relatively young aSAH population but also for society.

Implications

Some have questioned if a so-called good outcome justifies the assumption that aSAH patients have no relevant neurobehavioral impairments (Hütter et al., 1999). Our findings support the notion of an invisible dysfunction after aSAH. All our patients were good outcome (mRS 0–2) where majority had no signs of cognitive deficit, nevertheless, they experienced a debilitating and long-lasting fatigue, sometimes in conjunction with emotional problems, with a major impact on perceived quality of life and ability to return to work. This apparent discrepancy is of importance in clinical practice. It is crucial that clinicians early in the recovery process can identify and acknowledge that fatigue is distinct from normal exhaustion and may be part of a long-lasting illness trajectory with a huge impact on social and occupational engagement. The aSAH survivor and their families are in need of information about the prevalence and typical characteristics of post-aSAH fatigue in order to have a better foundation for realistic expectations regarding recovery and coping. Acknowledging post-aSAH fatigue as a health problem can facilitate coping.

Since our results support the notion of fatigue and depression as distinct entities, it appears sensible to treat the latter with antidepressants. A relief of depressive symptoms has the potential to reduce symptom severity of fatigue although not being a cure of fatigue *per se*. Fatigue as the predominant contributor of the inability of RTW will, however, not be affected by antidepressant treatment. Since physical fatigue and impairment is not a dominant problem, principles of stroke rehabilitation with a stronger focus on physical training may not be helpful or even counterproductive in aSAH patients (Johansson and Rönnbäck, 2014).

Our findings also highlight the need for more research. The present study emphasizes the need for more knowledge on the typical features of fatigue after aSAH. A better understanding of which fatigue features to focus on and how to measure these aspects in a standardized manner could generate empirical evidence about the ossible underlying mechanism of fatigue and will therefore endorse the development of evidence-based treatment for fatigue. To this date, there is still insufficient evidence to support the use of any intervention to treat or prevent fatigue after stroke (Wu et al., 2015).

Limitations

Our results have to be interpreted in light of the strict selection of participants based on the inclusion and exclusion criteria of the RCT they were recruited into. This resulted in all participants being good outcome (mRS 0–2) aSAH survivors without significant neurological or cognitive deficits. Furthermore, participation in our RCT, from where the present data were extracted, was comprehensive, many patients would have to travel over long distances to participate, and many patients, therefore, declined to participate. The RCT participants may thus have unknown common features affecting the profiles presently investigated. Nevertheless, since there were no

significant differences between included and excluded patients with regard to gender, aneurysm location, and mode of aneurysm repair, and as we included patients over the entire specter of aSAH severity (even more in poor grade than among those excluded), the present findings should be representative for all patients with post-aSAH fatigue. It appears paradoxical that the deadliest type of intracerebral hemorrhage results in more neurologically intact survivors than ischemic stroke; it underlines, however, that the post-aSAH fatigue group is diverse from the post-stroke group that often struggles with neurological deficits. Selecting patients with post-aSAH fatigue and significant neurological impairment may have produced a different nature of fatigue in our itemized analysis. On the other hand, including only good outcome patients pinpoints the detrimental effects of fatigue after aSAH.

There are no validated instruments to assess fatigue after aSAH. Although the mental features of fatigue are not properly measured with FSS, it is still the most frequently used questionnaire for evaluating fatigue in stroke studies due to its high internal consistency (Nadarajah et al., 2017). The MFS is a new questionnaire for assessing mental fatigue after mild TBI, and its psychometric properties are not extensively studied in the aSAH population. On the other hand, there are strong similarities to the clinical picture in the chronic phase after mild TBI and aSAH, suggesting that the MFS questionnaire may also be a useful tool in the evaluation of post-aSAH fatigue. The MFS incorporates items addressing cognitive complaints like "Concentration difficulties" (item 5), "Memory problems" (item 6), and "Slowness of thinking" (item 7) which are not directly linked to fatigue. The score on these items will hence increase the MFS sum score, without a higher score necessarily reflecting more fatigue. It is noteworthy that our patients scored all of these three items higher than 1.0 on average even though the majority of their neuropsychological test performances were within the normal range. The individual perception of cognitive problems may hence also be an aspect of fatigue. Future studies of fatigue after aSAH should therefore employ and validate the use of questionnaires that address the multidimensionality of post-aSAH fatigue.

Also, the BDI-II and to some extent the BAI contain items that could be experienced by patients with post-aSAH fatigue but not necessarily the symptoms for which the measures were developed. Although we attempted to correct for this overlap by setting a conservative cut-off for the BDI-II and BAI, the potential for symptom overlap still exists.

Conclusions

Good outcome patients with post-aSAH fatigue experienced their fatigue as being among the three most disabling symptoms and when characterizing their fatigue they emphasized the questionnaire items "low motivation," "mental fatigue," and "sensitivity to stress". Fatigue due to exercise was the least bothersome aspect of fatigue and weight gain was associated with depressive symptoms rather than the severity of fatigue. Although there is a strong association between post-aSAH fatigue and mood disorders, especially depression, the overlap is incomplete and our findings support the notion that these symptoms are distinct entities. Post-aSAH fatigue often exists without significant neurological or cognitive impairments but relates significantly to reduced HRQoL and contributes to a low rate of return to work.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because it provides information about an unpublished RCT study. Requests to access the datasets should be directed to Elin Western, elin.western@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional ethics committee (reference: 2016/2214). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EW, AS, and TN designed the research. EW, AS, WS, TK, and TN acquired the data. EW and AS analyzed the data. EW, AS, WS, and TN interpreted the results. EW drafted the manuscript. AS, WS, TK, and TN edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2021.633616/full#supplementary-material.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

III

JNS

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.

Clinical trial registration nos.: 2016-004739-19 (clinicaltrialsregister.eu) and NCT03209830 (clinicaltrials.gov)

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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.

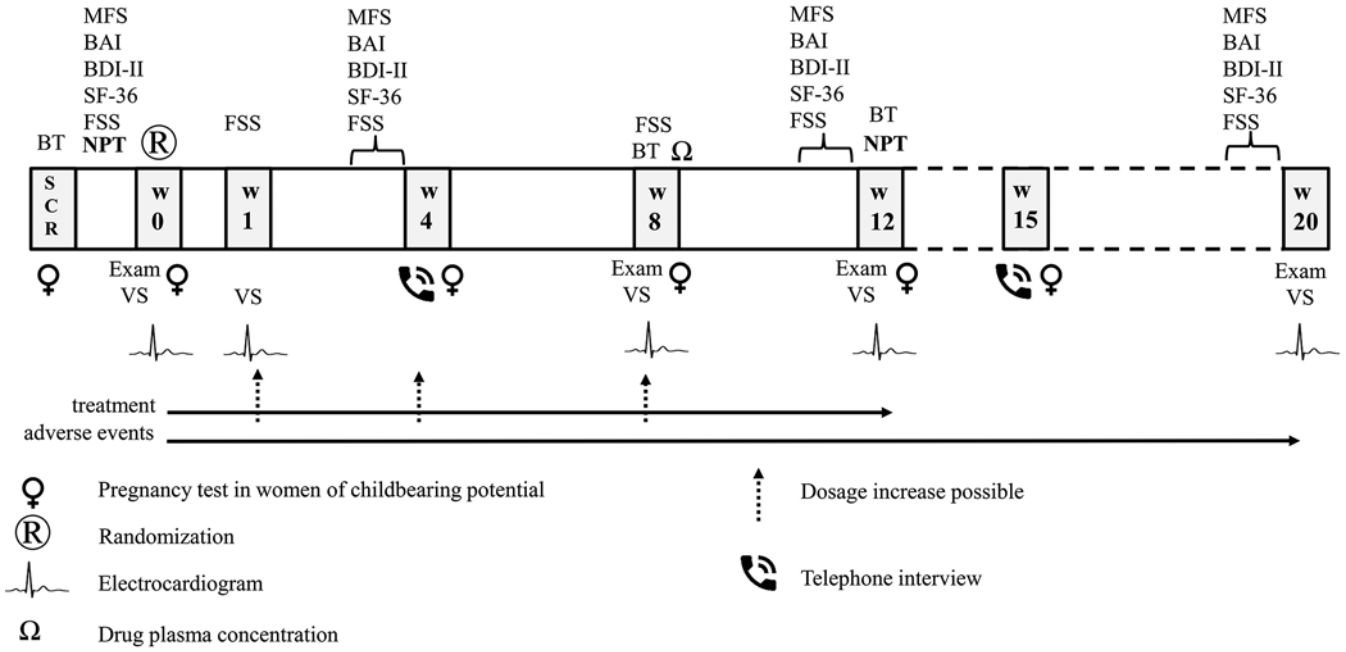

FIG. 1. Timeline of study procedures. Questionnaires: FSS, MFS, BAI, BDI-II, SF-36; BT = blood and urine tests; Exam = physical and neurological examination; NPT = neuropsychological test; SCR = screening; VS = vital signs; w = week; w20 = follow-up visit.

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

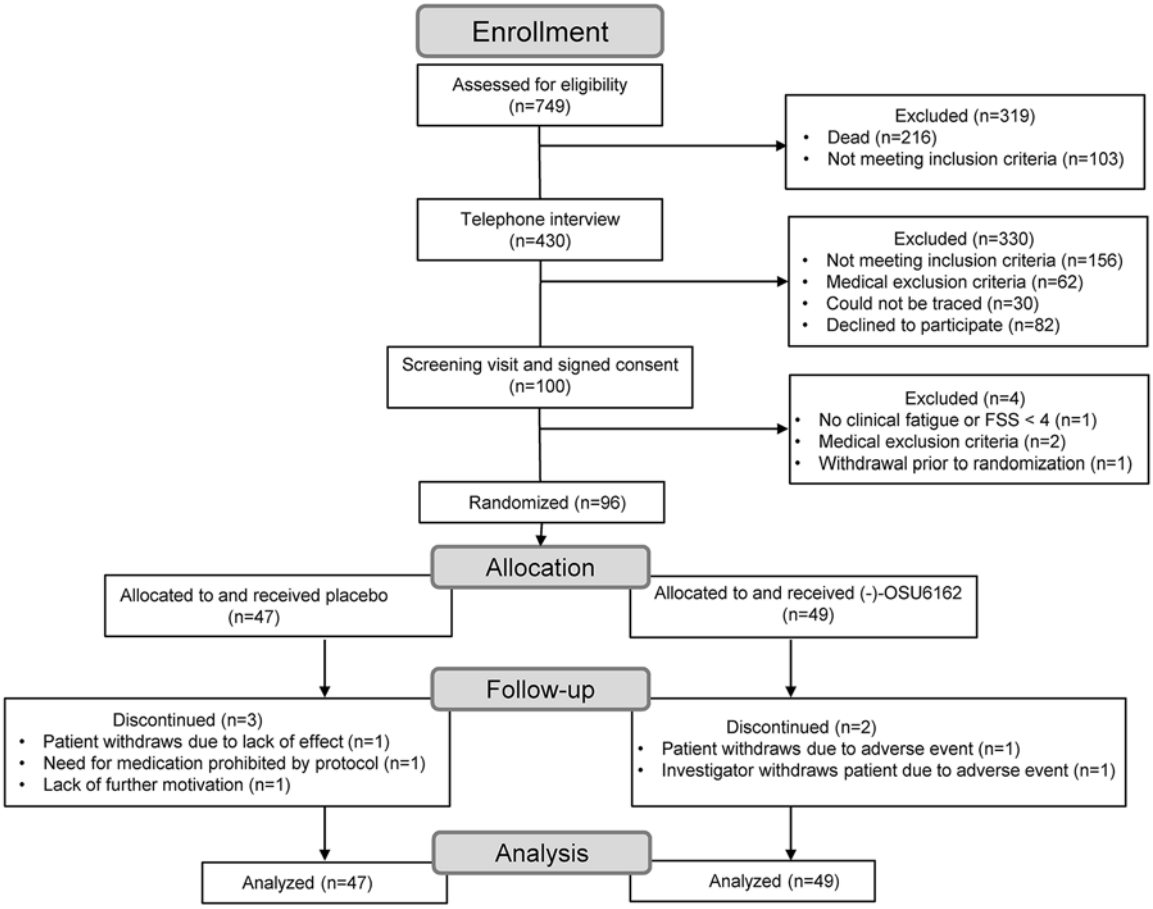

FIG. 2. Flowchart of eligible and included patients along with randomization to treatment with either (−)-OSU6162 or placebo.

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-

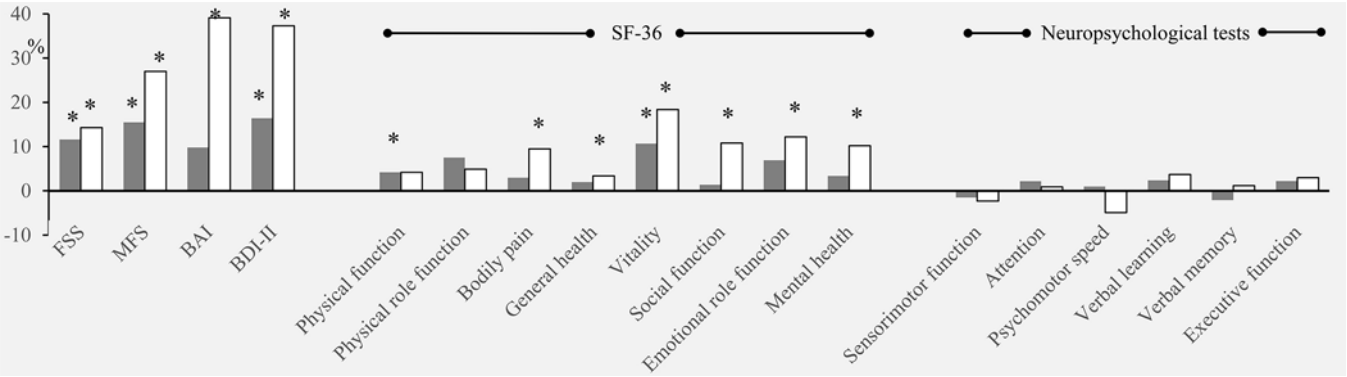

FIG. 3. Overview of percentage change from baseline to 12 weeks of treatment with (−)-OSU6162 (*dark columns*) or placebo (*white columns*) for the questionnaires FSS, MFS, BAI, BDI-II, the eight SF-36 domains, and the six domains of neuropsychological test performance. Improvement is shown as positive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

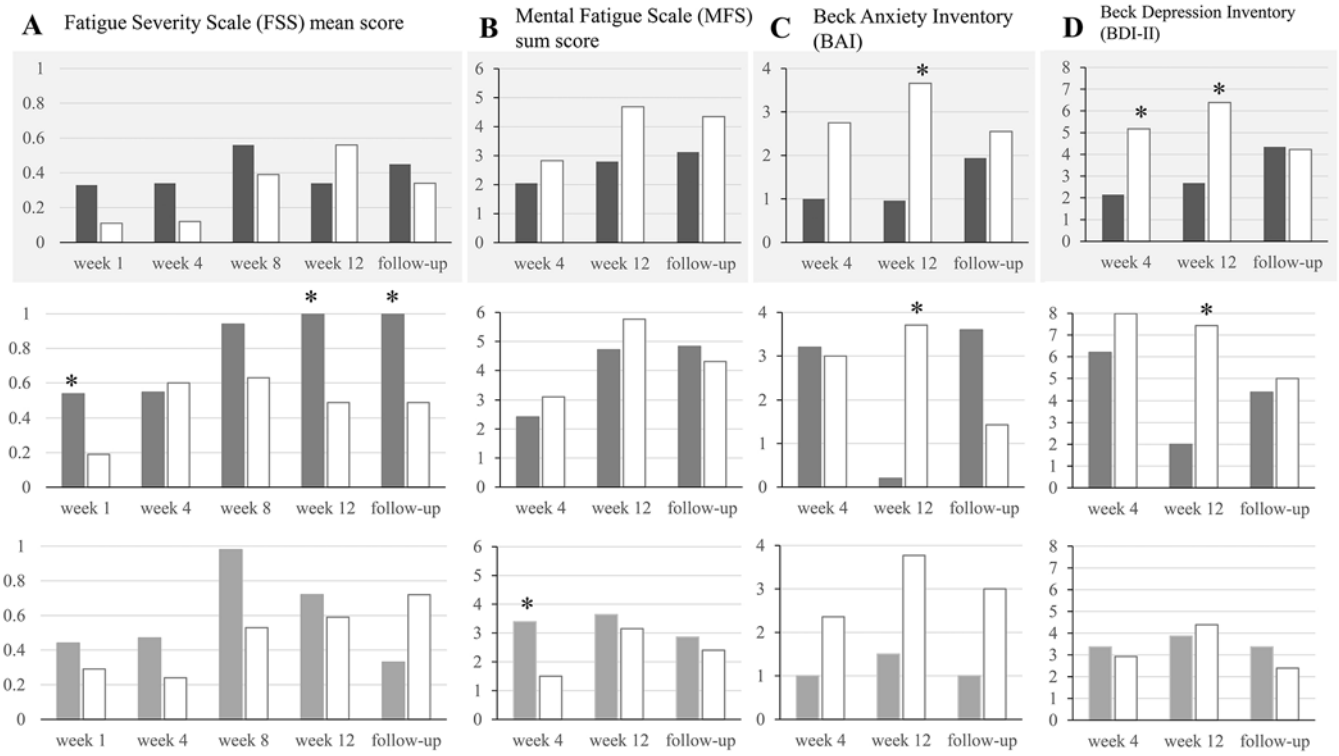

FIG. 4. Difference in points from baseline to the various times of assessment of the FSS mean score (**A**), MFS sum score (**B**), BAI score (**C**), and BDI-II score (**D**). The *upper panel* shows differences for all patients within treatment arms of (−)-OSU6162 (*dark columns*) and placebo (*white 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.

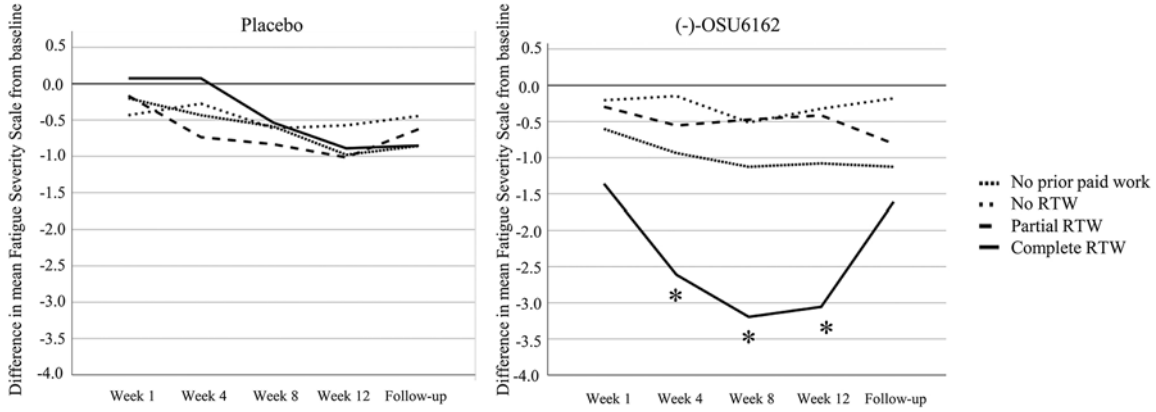

FIG. 5. Change in FSS mean score at 1, 4, 8, and 12 weeks of treatment with (−)-OSU6162 (*right*) or placebo (*left*) and at follow-up. Stratification into subgroups of those who had or did not have paid work at the time of ictus. Those who had paid work were further divided into those with no, partial,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

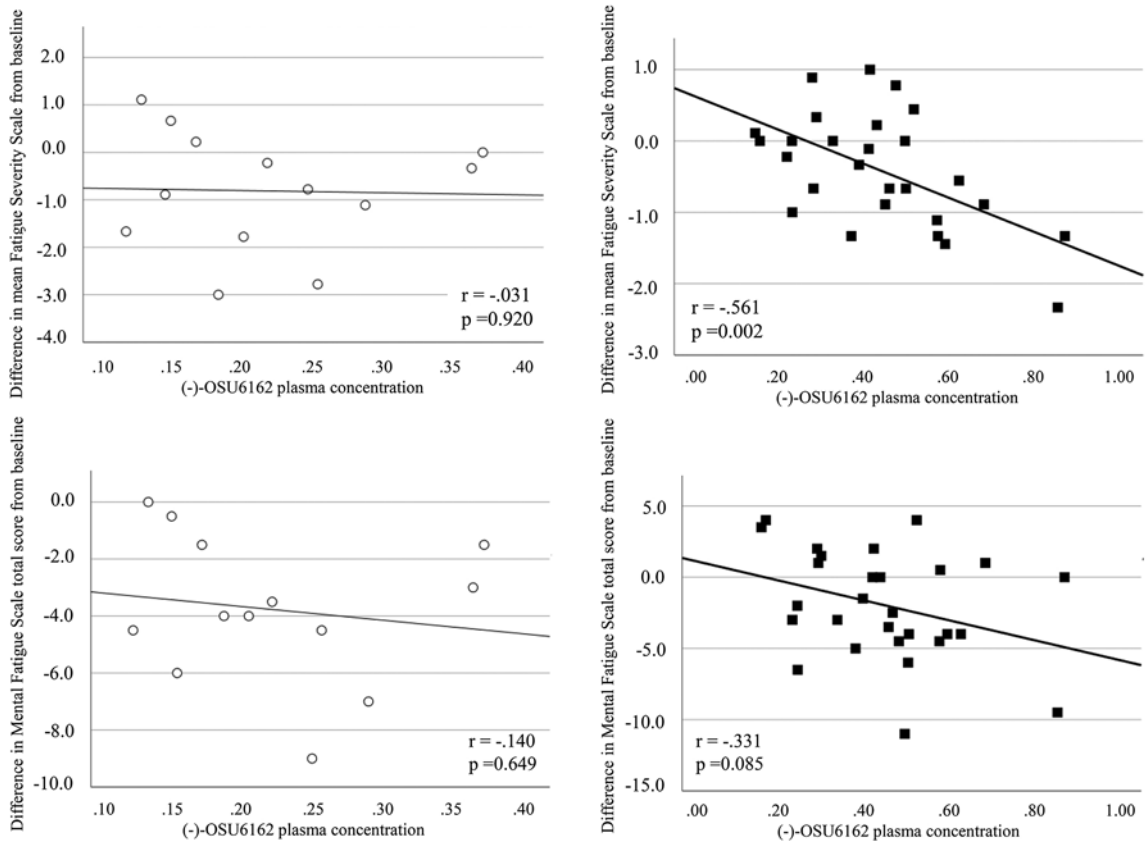

FIG. 6. Plasma concentration of (−)-OSU6162 in relation to decrease in FSS mean score (*upper*) and MFS sum score (*lower*) at week 8 stratified into study participants using 30 mg/day (15 mg × 2, *white circles, left*) and those using 60 mg/day (30 mg × 2, *black squares, right*). Pearson's correlation,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

Online-Only Content

Supplemental material is available with the online version of the article.

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8.5 Supplementary Table and Figure, Paper III

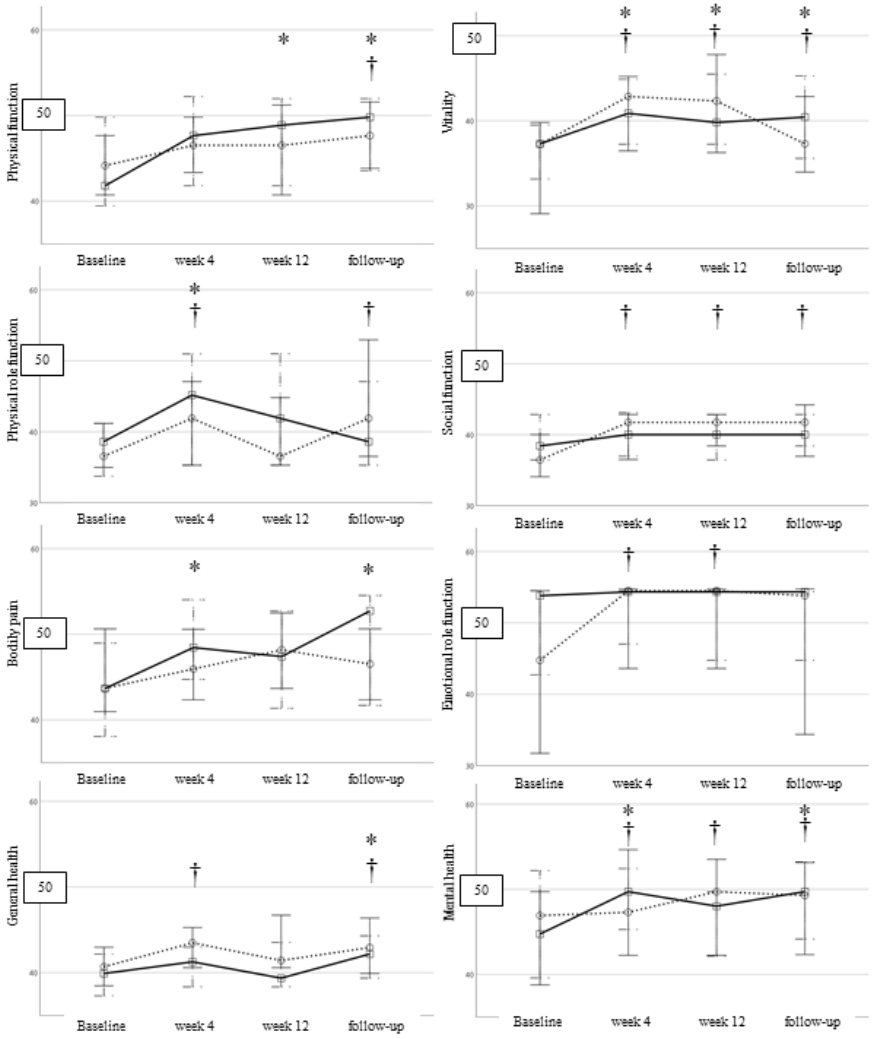
Supplementary Table 1 (paper III), neuropsychological test performance at baseline and after 12 weeks of treatment with (−)-OSU6162 or placebo. P-values are presented for changes from baseline within each treatment group. Bold letters indicate difference in test performance at baseline between treatment groups.

Neuropsychological test	(-)-OSU6162 (n=47) Median, IQR (z-score)			Placebo (n=44) Median, IQR (z-score)		
	baseline	Post treatment	P-value	baseline	Post treatment	P-value
Sensorimotor function						
Pegboard Dominant Hand	-0.30 (-1.40;0.10)	-0.50 (-1.10;0.30)	0.325	-0.70 (-1.20;0.23)	-0.20 (-1.20;0.98)	0.193
Pegboard Non-dominant Hand	-0.80 (-1.30;0.00)	-0.60 (-1.30;-0.10)	0.605	-0.60 (-1.20;-0.10)	-0.50 (-0.90;0.40)	0.134
D-KEFS, Trail making test 5	-0.35 (-1.35;0.00)	-0.35 (-0.65;0.00)	0.109	-0.35 (-1.00;0.00)	-0.35 (-1.00;0.26)	0.977
Attention						
D-KEFS, Trail Making test 1	0.00 (-0.65;0.35)	0.00 (-0.35;0.65)	0.162	0.00 (-0.65;0.65)	0.00 (-0.58;0.65)	0.461
WAIS-IV, Digit span forward	0.35 (-0.65;0.65)	0.35 (-0.35;0.65)	0.345	0.00 (-0.65;0.65)	0.18 (-0.65;0.35)	0.855
WAIS-IV, Digit span backward	0.00 (-0.35;0.35)	0.00 (-0.65;0.65)	0.724	0.00 (-0.35;0.65)	0.00 (-0,35;0.65)	0.848
WAIS-IV, Digit span sequence	0.00 (-1.00;0.65)	0.00 (-1.00;0.65)	0.989	0.00 (-0.35;0.58)	0.00 (-0.58;0.58)	0.760
CPT-III, Detectability	-0.20 (-1.10;0.70)	0.10 (-0.70;0.90)	0.001	-0.40 (-0.90;-0.03)	0.05 (-0.70;0.68)	0.000
CPT-III, Omissions	0.20 (-0.50;0.50)	0.40 (-0.20;0.60)	0.003	0.15 (-0.95;0.40)	0.30 (0.10;0.50)	0.006
CPT-III, Commissions	0.20 (-0.60;0.70)	0.30 (-0.60;0.70)	0.069	-0.25 (-0.88;0.28)	0.15 (-0.20;0.60)	0.002
Psychomotor speed						
D-KEFS, Trail Making test 2	0.35 (-0.35;1.00)	0.65 (0.00;1.00)	0.101	0.65 (-0.26;0.65)	0.35 (-0.35;1.00)	0.506
D-KEFS, Trail Making test 3	0.35 (0.00;0.65)	0.65 (0.00;1.00)	0.274	0.35 (-0.58;0.91)	0.65 (-0.26;1.00)	0.399

D-KEFS, Color word interference test 1	-0.35 (-1.00;0.35)	-0.35 (-1.00;0.35)	0.870	-0.18 (-1.00;0.35)	0.00 (-0.65;0.35)	0.004*
D-KEFS, Color word interference test 2	-0.65 (-1.35;0.00)	-0.42 (-1.00;0.35)	0.036	-0.35 (-0.65;0.35)	-0.35 (-0.65;0.35)	0.971
Verbal learning						
CVLT, Learning Total 1-5	-0.30 (-1.30;0.50)	-0.40 (-1.10;0.60)	0.947	-0.30 (-1.08;0.50)	-0.10 (-1.00;0.60)	0.334
CVLT, Learning Trial 1	-1.00 (-1.50;-0.50)	-1.00 (-2.00;0.00)	0.526	-0.50 (-1.00;0.00)	-0.50 (-1.38;0.00)	0.245
CVLT, List B	-1.00 (-1.50;0.00)	-1.00 (-1.50;-0,50)	0.407	-1.00 (-1.38;-0.13)	-1.00 (-1.00;-0.50)	0.991
Verbal memory						
CVLT, recognition hits	0.00 (-0.50;0.50)	-0.00 (-1.00;0.50)	0.616	-0.00 (-1.00;0.50)	-0.00 (-1.00;0.50)	0.517
CVLT, recognition false positive	-0.20 (-1.00;0.50)	-0.50 (-1.00;0.50)	0.166	-0.10 (-0.50;1.00)	-0.50 (-1.00;1.00)	0.073
CVLT, list A short term	-0.50 (-1.00;0.50)	0.00 (-1.50;0.50)	0.559	-0.20 (-1.00;0.50)	-0.60 (-1.38;0.00)	0.030
CVLT, list A long term	-0.30 (-1.00;0.50)	-0.50 (-1.50;0.50)	0.164	-0.20 (-1.00;0.50)	-0.65 (-1.38;0.00)	0.001
Executive function						
D-KEFS, Trail making test 4	0.35 (-0.65;0.65)	0.35 (-0.35;0.65)	0.100	0.35 (-0.35;0.65)	0.35 (-0.26;0.65)	0.115
D-KEFS, Color word interference test 3, reaction time	0.00 (-0.65;0.65)	0.35 (0.00;1.00)	0.015	0.35 (-0.58;1.00)	0.50 (-0.35;1.00)	0.025
D-KEFS, Color word interference test 4, reaction time	-0.35 (-1.00;0.65)	0.35 (-0.65;0.65)	0.001*	0.35 (-0.58;0.65)	0.35 (-0.58;0.65)	0.495

*: significant improvement compared to the other treatment group; IQR: interquartile range; CLVT-II: California Verbal Learning Test 2nd edition; CPT-III: Conners' Continuous Performance 3rd edition; WAIS-IV: Wechsler Adult Intelligence Scale 4th edition; D-KEFS: Delis-Kaplan Executive Function System

Supplementary Figure 1 (paper III).



Supplementary Fig.1

Health-related quality of life measured with the Short-form 36 (SF-36) at baseline, 4 and 12 weeks of treatment, and at follow-up. The physical domains physical function, physical role function, bodily pain, and general health to the left. The mental domains vitality, social function, emotional role function and mental health to the right.

Solid line: (-)-OSU6162 group
Dotted line: placebo group

Median with 95% confidence interval. A value of 50 corresponds to the sex and age adjusted norm.

*: significant change from baseline in the (-)-OSU6162 group; †: significant change from baseline in the placebo group