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Published on: 16 Nov 2010 - Neurology (Lippincott Williams & Wilkins)

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Kaiser, P R ; Valko, P O ; Werth, E ; Thomann, J ; Meier, J ; Stocker, R ; Bassetti, C L ; Baumann, C R

Abstract: **BACKGROUND:** Excessive daytime sleepiness (EDS) and fatigue are common symptoms after traumatic brain injury (TBI), but there is no specific treatment for affected patients. With this pilot study, we aimed at studying the effect of daily modafinil on posttraumatic EDS and fatigue. **METHODS:** We conducted a prospective, double-blind, randomized, placebo-controlled pilot study in 20 patients with TBI who had fatigue or EDS or both. After baseline examinations (questionnaires including the Epworth Sleepiness Scale to assess EDS and the Fatigue Severity Scale to assess fatigue, actigraphy, polysomnography, maintenance of wakefulness test, and psychomotor vigilance test), 10 patients received 100 to 200 mg modafinil every morning, and 10 patients were treated with placebo. After a 6-week treatment period, all examinations were repeated. **RESULTS:** EDS improved significantly in patients with TBI who were treated with modafinil, compared with the placebo group. Similarly, the ability to stay awake on the maintenance of wakefulness test improved only in the modafinil group. Modafinil, however, had no impact on posttraumatic fatigue. Clinically relevant side effects were not observed. **CONCLUSION:** This study indicates that modafinil is effective and well tolerated in the treatment of posttraumatic EDS but not of fatigue. **CLASSIFICATION OF EVIDENCE:** This study provides Class I evidence that modafinil (100-200 mg daily) improves posttraumatic EDS compared with placebo. This study provides Class I evidence that modafinil (100-200 mg daily) does not improve posttraumatic fatigue compared with placebo.

DOI: <https://doi.org/10.1212/WNL.0b013e3181fd62a2>

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ZORA URL: <https://doi.org/10.5167/uzh-43366>

Journal Article

Published Version

Originally published at:

Kaiser, P R ; Valko, P O ; Werth, E ; Thomann, J ; Meier, J ; Stocker, R ; Bassetti, C L ; Baumann, C R (2010). Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology*, 75(20):1780-1785.

DOI: <https://doi.org/10.1212/WNL.0b013e3181fd62a2>

Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury



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ABSTRACT

Background: Excessive daytime sleepiness (EDS) and fatigue are common symptoms after traumatic brain injury (TBI), but there is no specific treatment for affected patients. With this pilot study, we aimed at studying the effect of daily modafinil on posttraumatic EDS and fatigue.

Methods: We conducted a prospective, double-blind, randomized, placebo-controlled pilot study in 20 patients with TBI who had fatigue or EDS or both. After baseline examinations (questionnaires including the Epworth Sleepiness Scale to assess EDS and the Fatigue Severity Scale to assess fatigue, actigraphy, polysomnography, maintenance of wakefulness test, and psychomotor vigilance test), 10 patients received 100 to 200 mg modafinil every morning, and 10 patients were treated with placebo. After a 6-week treatment period, all examinations were repeated.

Results: EDS improved significantly in patients with TBI who were treated with modafinil, compared with the placebo group. Similarly, the ability to stay awake on the maintenance of wakefulness test improved only in the modafinil group. Modafinil, however, had no impact on posttraumatic fatigue. Clinically relevant side effects were not observed.

Conclusion: This study indicates that modafinil is effective and well tolerated in the treatment of posttraumatic EDS but not of fatigue.

Classification of evidence: This study provides Class I evidence that modafinil (100–200 mg daily) improves posttraumatic EDS compared with placebo. This study provides Class I evidence that modafinil (100–200 mg daily) does not improve posttraumatic fatigue compared with placebo.

Neurology® 2010;75:1780–1785

GLOSSARY

EDS = excessive daytime sleepiness; **ESS** = Epworth Sleepiness Scale; **FSS** = Fatigue Severity Scale; **GCS** = Glasgow Coma Scale; **MWT** = maintenance of wakefulness test; **TBI** = traumatic brain injury.

Traumatic brain injury (TBI) occurs in about 1.4 million people in the United States each year, corresponding to an incidence of 460 per 100,000 per year.¹ Another study estimated that 3.17 million US citizens (more than 1% of the total US population) have long-term neurologic disability that resulted from TBI.² Thus, TBI causes the largest number of disability-adjusted life-years lost to death and to varying degrees of disability, including posttraumatic sleep-wake disturbances.³

Excessive daytime sleepiness (EDS) and fatigue are frequent symptoms after TBI. In our prospective study on posttraumatic sleep-wake disturbances, we studied 65 consecutive patients by means of questionnaires and sleep laboratory examinations 6 months after trauma.⁴ We found EDS in 38% and fatigue in 17% of our patients. Our findings are in line with other reports on posttraumatic sleep-wake disturbances.^{5–7} The etiology of posttraumatic EDS is not known. Recently, we found a partial loss of wake-promoting hypothalamic hypocretin (orexin) neurons after fatal TBI.⁸ EDS and fatigue significantly impair quality of life and daytime functioning, including professional performances and social activities.⁴ Despite their high inci-

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*The first 2 authors contributed equally to this study.

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Study funding: Supported by Schweizerischer Versicherungsverband (SVV), Zurich, Switzerland, and Cephalon GmbH, Martinsried, Germany.

Disclosure: Author disclosures are provided at the end of the article.

dences, posttraumatic EDS and fatigue are still underestimated, and there is no treatment for affected patients.

Thus, with this pilot study, we aimed at studying the effect of daily modafinil on posttraumatic EDS and fatigue. Modafinil (2-[(diphenylmethyl) sulfinyl] acetamide) has wake-promoting properties and is approved by the US Food and Drug Administration for the treatment of EDS in patients with narcolepsy, obstructive sleep apnea syndrome, and shift work sleep disorder.

METHODS This prospective study was conducted at the Department of Neurology of the University Hospital of Zurich, Switzerland, between January 2007 and June 2009.

Subjects. In this prospective, double-blind, randomized, placebo-controlled pilot study, we included 20 consecutive patients from our first study on posttraumatic sleep-wake disturbances.⁴ All patients were admitted for closed mild to severe TBI to our surgical intensive care unit, where they were recruited for this study. TBI severity was quantified with the initial Glasgow Coma Scale (GCS) examination, which was performed immediately after trauma (mild TBI: GCS 13–15, moderate TBI: GCS 9–12, severe TBI: GCS 3–8). Admission to the surgical intensive care unit was for mild to severe TBI. The mandatory inclusion criterion was the presence of fatigue or EDS or both since TBI. Patients with neurologic, psychiatric, or other disorders and medication that might cause sleep-wake disturbances were not included. Furthermore, we excluded patients who revealed significant sleep-wake disturbances other than posttraumatic vigilance impairment at baseline examinations. Patients with chronic sleep deprivation were also excluded. The latter was diagnosed in patients with EDS who slept ≥ 2 hours more on weekends or during holidays than during weekdays. All exclusions were made before randomization.

Fatigue was assessed with the Fatigue Severity Scale (FSS), and EDS was assessed with the Epworth Sleepiness Scale (ESS). Both scales have been validated in German.^{9,10} Fatigue is diagnosed in patients with FSS values above 4.0, and EDS is diagnosed in those with ESS scores ≥ 10 . Before randomization, written informed consent was obtained from all patients.

Baseline examinations. At baseline, patients were administered the Beck Depression and Anxiety Inventory, a standard questionnaire to assess depression and anxiety symptoms.¹¹ To rule out chronic sleep deprivation, patients were examined by 2 weeks of actigraphy studies. Actigraphy is a noninvasive method to monitor activity/rest cycles over a defined period of time. Sleep and physical activity levels were recorded by wrist actigraphy. The actimeter includes a light sensor and is worn on the nondominant wrist (Actiwatch, CamNtech Ltd., Cambridge, UK).¹² With this software, the determination of time asleep and time awake relies on an algorithm using the activity data recorded by the Actiwatch in a series of linked calculations. During actigraphy recordings, all patients simultaneously filled in sleep logs.

Immediately after actigraphy, conventional nocturnal polysomnography was recorded from 11 PM to 7 AM. We used a 16-channel recording system (Embla A10, Embla, Broomfield,

CO). Sleep-stage scoring was performed visually by the first authors according to standard criteria.¹³ Patients with significant sleep-wake disturbances, such as obstructive sleep apnea, detected during polysomnographic recordings were excluded from the study. The day after polysomnography, all patients were examined by a maintenance of wakefulness test (MWT).¹⁴ This test measures the ability to stay awake for 40 minutes while sitting quietly in a dark room and is performed every 2 hours, in total 4 times a day. Mean sleep latency in the MWT was defined as the time from lights off to the first epoch of any sleep stage. At the same day, before every MWT test, we examined the patients' vigilance with the psychomotor vigilance test. This test measures reaction times of patients to the sudden appearance of a time-keeper on a black computer screen.¹⁵ The test lasts 10 minutes and assesses the number of lapses, defined as times the subject does not respond to the signal in time, and calculates reaction times. Intake of caffeine and medication with known effects on vigilance and sleepiness were not allowed during days and nights with sleep recordings and vigilance tests.

Randomization and follow-up examinations. After completion and evaluation of all tests, included patients were randomly assigned to either the modafinil group or the placebo group. All study procedures were performed in a strict double-blind manner. For allocation concealment, labeling of masked study medication (modafinil or placebo) by manufacturing of numbered containers was performed centrally by the Pharmacy of the University Hospital of Zurich. All patients in the treatment group started with 1 oral capsule (corresponding to 100 mg modafinil per day in the treatment group), administered in the morning. Every 2 weeks, a phone call from the first author evaluated the subjective response to treatment, including efficacy and side effects. In patients without clear efficacy and without side effects, the dose was doubled: 1 oral capsule in the morning and 1 at noon. In patients with troublesome side effects with 2 capsules, there was a possibility to reduce the dose again. Furthermore, all patients were asked whether they estimated their vigilance impairment to be ameliorated by treatment.

After 6 treatment weeks, all examinations, including questionnaires, actigraphy, conventional nocturnal polysomnography, MWTs, and psychomotor vigilance tests, were repeated. Primary outcome measures included improvements in FSS and ESS values, and in mean sleep latencies on MWT.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethical standards committee on human experimentation (Ethikkommission des Kantons Zurich) and by Swissmedic, the Swiss agency for therapeutic products. All study participants gave oral and written consent to all study procedures.

Statistics. Statistical analyses were performed by using correlation analyses (Pearson and Spearman), Student *t* tests, Mann-Whitney *U* tests, and multivariate regression analyses. Parametric tests were 2-tailed.

RESULTS Demographic data and baseline characteristics of both the treatment and the placebo group can be found in table 1. Patients in both groups did not differ in age, sex distribution, severity of TBI, or duration since trauma. At study inclusion, the duration since trauma was 1 to 3 years in all patients. After baseline examinations, we excluded 4 patients because of obstructive sleep apnea and 1 patient be-

Table 1 Baseline characteristics and changes from baseline in 20 patients with traumatic brain injury, 10 treated with placebo and 10 treated with modafinil^a

	Placebo	Modafinil	p Value
General findings			
Age, y	43 ± 19	37 ± 9	
Sex, % male	90	80	
Glasgow Coma Scale	8 ± 4	7 ± 4	
Pathologic CT findings, %	60	50	
Interval after trauma, y	2.0 ± 1.2	1.8 ± 0.9	
High dosage (modafinil group: 200 mg), %	80	80	
Side effects, %	10	20	
Baseline findings			
ESS	8.2 ± 3.7	10.0 ± 4.2	
FSS	5.0 ± 1.4	4.6 ± 0.8	
Beck Depression Inventory	11 ± 9	9 ± 6	
Beck Anxiety Inventory	10 ± 11	10 ± 9	
PSG: sleep efficiency, %	87 ± 5	88 ± 11	
PSG: sleep latency to NREM2, min	20 ± 16	16 ± 18	
PSG: apnea-hypopnea index	4.3 ± 3.8	2.6 ± 3.3	
PSG: periodic limb movements index	0.8 ± 0.9	2.1 ± 4.4	
MWT: mean sleep latency, min	18.7 ± 9.3	15.6 ± 11.4	
Actigraphy: awake per 24 h, %	39 ± 13	41 ± 11	
Actigraphy: sleep elongation weekend, h	0.5 ± 0.7	0.8 ± 1.0	
PVT: velocity, s	3.7 ± 0.6	3.8 ± 0.5	
PVT: no. of lapses	3.7 ± 4.3	2.8 ± 1.9	
Changes from baseline			
ESS	0.7 ± 1.8	-2.3 ± 2.3	0.005 ^b
FSS	0.0 ± 0.6	-0.8 ± 1.0	0.07 ^b
Beck Depression Inventory	-0.4 ± 3.5	1.1 ± 3.2	NS
Beck Anxiety Inventory	0.5 ± 5.2	-0.1 ± 1.8	NS
PSG: sleep efficiency, %	0.8 ± 5.7	0.0 ± 5.1	NS
PSG: sleep latency to NREM2, min	-13.6 ± 16.4	2.7 ± 14.7	0.03 ^b
MWT: mean sleep latency, min	0.4 ± 6.2	8.4 ± 9.6	0.04 ^b
Actigraphy: awake per 24 h, %	-0.3 ± 4.7	1.9 ± 3.8	NS
PVT: velocity, s	0.0 ± 0.2	-0.2 ± 0.4	NS
PVT: no. of lapses	0.8 ± 2.9	1.3 ± 2.6	NS

Abbreviations: ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MWT = maintenance of wakefulness test; NS = not significant; PSG = polysomnography; PVT = psychomotor vigilance test.

^a Mean values are given with SDs.

^b Mann-Whitney *U* test.

cause of chronic sleep deprivation. A flow diagram depicting the passage of participants through this study is given in figure 1.

At baseline, 8 patients in every group were diagnosed with fatigue. FSS values at baseline did not differ between the 2 groups: mean FSS values were 5.0 ± 1.4 in the modafinil group and 4.6 ± 0.8 in the placebo group. Five patients in the placebo group and 6 in the modafinil group were diagnosed with

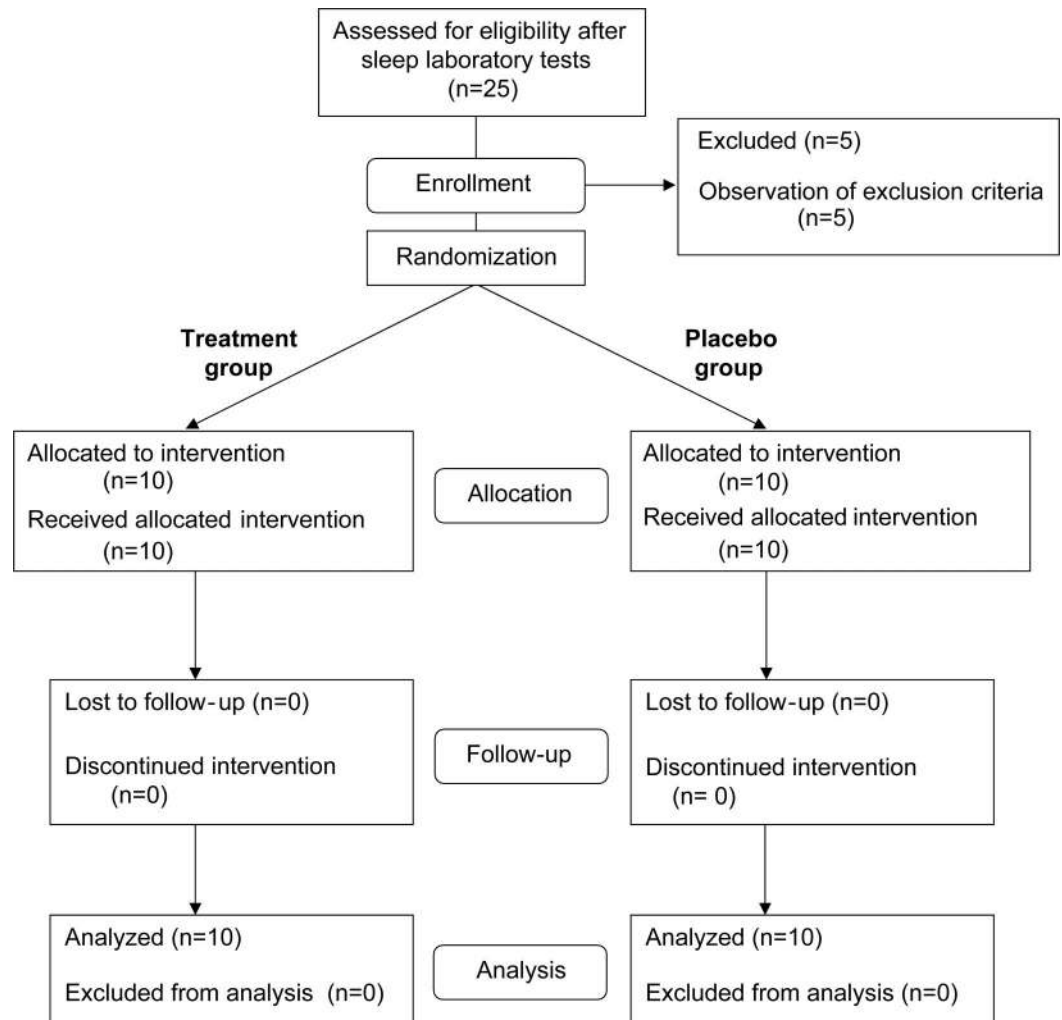
EDS. Again, ESS values at baseline did not differ between the 2 groups (modafinil: 8.2 ± 3.7, placebo: 10.0 ± 4.2). Relevant sleep-related breathing or movement disorders were not present in either group. The respective measures such as the apnea-hypopnea index or the periodic limb movement index were similar in the 2 groups. Also, actigraphy measures did not differ between groups. Beck Depression and Anxiety Inventories revealed similar results in the 2 groups. In both treatment groups, the dose of study medication was doubled in 8 patients. It was not necessary in any of these patients to reduce the dose again because of side effects. None of our patients discontinued treatment.

After 6 weeks of treatment, the decrease in FSS scores was higher in the modafinil group (-0.8 ± 1.0) than in the placebo group (0.0 ± 0.6), but this finding was not significant after correction for the independent variables sex, age, TBI severity, and Beck Depression and Anxiety scale values (figure 2). Fatigue was still present in all 8 patients in the placebo group and in 4 patients in the modafinil group. When selecting only patients with fatigue (FSS ≥ 4.0) at baseline, decreases in FSS scores were not higher in the modafinil group.

After 6 treatment weeks and compared with the placebo group, the decrease in ESS scores was higher in the modafinil group (-2.3 ± 2.3 compared with 0.7 ± 1.8, *p* = 0.005; figure 2). This finding remained significant after correction for the same independent variables, and also when selecting only those patients with EDS (ESS ≥ 10) at baseline. Under treatment, EDS was still present in 3 patients in each group.

The objective measurement of the ability to remain awake at daytime under nonstimulating conditions revealed a significant increase compared with baseline of the mean sleep latency on MWT in the treatment group (8.4 ± 9.6 minutes) compared with the placebo group (0.4 ± 6.2 minutes) (*p* = 0.04; figure 2). Patients under placebo treatment fell asleep quicker at nocturnal polysomnography than at baseline (-13.6 ± 16.4 minutes) after 6 treatment weeks, which probably reflects habituation to the sleep laboratory environment. Patients treated with modafinil, however, had no change in sleep latencies compared with baseline (2.7 ± 14.7 minutes), which again indicates decreased sleep pressure compared with the placebo group (*p* = 0.03). Conversely, the psychomotor vigilance test did not reveal differences between the groups: both reaction times and number of lapses were similar. Actigraphy revealed an increase of time awake per 24 hours in the modafinil group by 1.9 hours, whereas time awake decreased mildly (-0.3 hours) in the placebo group (*p* = 0.33).

Figure 1 Flow diagram depicting the passage of participants through this randomized controlled trial



The overall subjective estimation of patients on vigilance impairment amelioration was similar in the 2 groups (table 2). These subjective self-estimations did not correlate with the FSS, the ESS, or MWT results. Depression and anxiety scale values did not change from baseline in either group. Thus, treatment—although improving objective measures of sleepiness—had no impact on quality of life. This may not be surprising, because 2.3 points on the ESS is not clinically significant, although 8.4 minutes on the MWT might be.

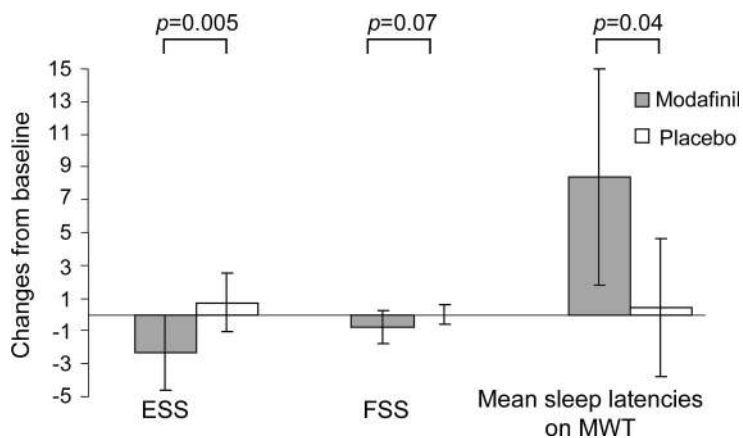
Side effects were similar in the 2 groups. One placebo patient reported a reduction in appetite, 1 modafinil patient reported nausea and mild and transient stomachache, and 1 modafinil patient reported mild arthralgia in the shoulders.

DISCUSSION The main outcome of this first double-blind, randomized, placebo-controlled study that included electrophysiologic sleep laboratory tests in 20 patients with TBI indicates that 100 to 200 mg

modafinil is effective and well tolerated in the treatment of posttraumatic EDS but not of fatigue. ESS values decreased by 2.3 points and mean sleep latencies on MWT increased by 8.4 minutes under treatment. Furthermore, patients with TBI who were treated with modafinil stayed awake 1.9 hours longer per day, whereas placebo-treated patients did not reveal an increase of their time awake. This potentially important difference, however, remained nonsignificant in this small trial.

Several studies observed an improvement of EDS with modafinil in a variety of disorders, including narcolepsy, obstructive sleep apnea, and chronic shift work.¹⁶⁻¹⁸ After TBI, EDS and fatigue are frequent complications.⁴ Earlier studies showed a potential benefit of modafinil for the treatment of posttraumatic vigilance impairment.^{19,20} Under treatment with 100 to 400 mg modafinil (once every morning), Teitelman reported increased wakefulness and attention of posttraumatic hypersomnia in 10 patients who had closed TBI.¹⁹ Unfortunately, objective mea-

Figure 2 Changes from baseline in ESS and FSS values, and in mean sleep latencies on MWT (in minutes)



ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MWT = maintenance of wakefulness test.

asures such as MWT or mean sleep latency tests were not performed, and study results were not controlled.

Our findings contrast with a recent randomized questionnaire-based trial in more than 50 patients with TBI who had posttraumatic EDS.²⁰ These authors did not find a beneficial effect of 400 mg modafinil on fatigue and EDS. However, in this study, electrophysiologic sleep laboratory studies including polysomnography and vigilance tests have not been performed, and other possible causes of vigilance impairment have not been excluded by actigraphy. Furthermore, increased FSS or ESS scores at baseline were not mandatory for inclusion in the study. Because of these methodologic differences, it is not possible to compare this study with our own trial. In our trial as much as in this cited study, however, there is the possibility of a ceiling effect, where no higher dose of modafinil would further improve vigilance in our patients. However, because we only administered 100 to 200 mg, we cannot rule out that higher doses might add benefit for our patients.

In our study, the subjective estimation of treated patients regarding an improvement of vigilance during medication was not different from those who re-

ceived placebo. This may have 2 reasons: First, based on findings in our earlier studies and in accordance with other authors, we believe that many patients with TBI tend to underestimate their sleep problems.^{4,21} In our first study on posttraumatic sleep-wake disturbances, we found very low mean sleep latencies on multiple sleep latency tests in patients with TBI who reported that they would not be sleepy at daytime.⁴ Likewise, in the present study, the effect of modafinil on ESS values is smaller than in trials examining patients with narcolepsy or sleep apnea, whereas the improvement on the MWT is similar to the findings in these disorders.^{16,17} Therefore, the question whether patients with TBI develop a specific type of anosognosia toward sleep-wake disturbances remains to be elucidated in systematic studies. Second, in this pilot study, we administered only 100 to 200 mg modafinil. We assume that higher doses might have a higher and clinically more significant impact on vigilance.

The lacking effect of modafinil on fatigue is remarkable. Recently, a similar outcome was observed in patients with Parkinson disease, with an improvement of EDS but not of fatigue with modafinil treatment.²² In fatigue related to multiple sclerosis or diencephalic stroke, however, modafinil was effective.²³ In general, fatigue is an ill-defined symptom that probably is influenced by several factors, including physical exhaustibility, sleep-wake disturbances, and disorders of mood. Furthermore, it is not clear whether fatigue and EDS belong to the same clinical spectrum. Our result of effectiveness of modafinil for EDS but not fatigue indicates that the 2 symptoms are distinct entities, probably with different pathophysiologic pathways.

AUTHOR CONTRIBUTIONS

Statistical analyses were performed by Christian R. Baumann.

DISCLOSURE

Dr. Kaiser, Dr. Valko, Dr. Werth, Ms. Thomann, and Ms. Meier report no disclosures. Prof. Stocker has served on scientific advisory boards for KCI Europe Holding BV and Baxter International Inc.; has received funding for travel or speaker honoraria from Fresenius Medical Care and Bio-Synthesis Inc.; and receives research support from the Swiss National Foundation, SUVA Foundation, the Swiss Academy for Medical Sciences, and Swisstransplant. Prof. Bassetti serves as Chief Editor of the *Swiss Archives of Neurology and Psychiatry* and on the editorial boards of the *Journal of Sleep Research*, *Sleep Medicine*, *Somnology*, and the *Belgian Neurological Journal*; has served on scientific advisory boards for and received speaker honoraria from Boehringer Ingelheim, Lundbeck Inc., Novartis, Pfizer Inc, ResMed Inc., and UCB; receives research support from Lundbeck Inc., Respiration, Inc., ResMed Inc., Vifor Pharma, and UCB; and receives institutional research support from the Zurich Center for Integrative Human Physiology and the Swiss National Science Foundation. Dr. Baumann has served on scientific advisory boards for and received speaker honoraria from Boehringer Ingelheim, UCB, and GlaxoSmithKline; receives research support from UCB, Cephalon, and Novartis; and receives institutional research support from the Swiss National Foundation.

Table 2 Overall subjective estimation of vigilance impairment (fatigue, excessive daytime sleepiness) amelioration

	Placebo	Modafinil	p Value (χ^2)
Much better	1	0	0.23
Better	1	3	
Somewhat better	1	3	
Unchanged	7	3	
Worse	0	1	

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