The effect of modafinil on fatigue, cognition, depression and quality of life in patients with a primary brain tumor

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Utrecht University

Fiore Giuseppin
Studentnr.: 3159418
Supervisor UU: dr. E. van den Berg
Supervisor VU: drs. F.W. Boele

Abstract

Cognitive deficits and psychological complaints are common in patients with primary brain tumors. Very little is known about the effect of modafinil of these symptoms. With the present double-blind placebo controlled crossover trial we investigated the effect of modafinil on fatigue, cognitive functioning, depression and overall QOL in patients with a primary brain tumor. Thirty-seven patients with heightened levels of fatigue enrolled in the study. Participants completed neuropsychological tests and self-report questionnaires of fatigue, mood, neurological functioning and QOL at baseline, after six weeks of modafinil or placebo treatment and after another six weeks of treatment. The results showed that modafinil seemed to improve working memor, but it increased the severity of fatigue and decreased the patient-reported sustained attention. On several measures of fatigue, cognition, mood and QOL, a placebo-effect was found. More research is required to be more definitive about the present findings. Future research should include a larger sample size and the making of a distinction in tumor type. Since the results of the present study show no major effects of modafinil, other options of pharmaceutical and psychological treatment should also be explored.

Introduction

Primary brain tumors account for 2% of all malignancies (Giordana & Clara, 2006). Cancer registry data in Europe show an incidence of 5 to 13 cases per year per 100,000 inhabitants in women and 7 to 11 cases a year in men (Bartolo et al., 2011). Primary brain tumors are second only to stroke as a cause of death attributable to neurologic disorders (Giordana & Clara, 2006).

Primary brain tumors are classified depending on the exact site of the tumor, the type of tissue involved, and whether they are malignant or benign (American Brain Tumor Association, 2012). Meningiomas are the most common benign brain tumor and originate in the dura that covers the brain and spinal chord (Buckner et al., 2007). The most common malignant brain tumors are gliomas. Gliomas come from glial cells such as astrocytes, oligodendrocytes and ependymocytes (American Brain Tumor Association, 2012). Most gliomas originate from astrocytes. These tumors are graded on a scale from I to IV based on how normal or abnormal the cells look. There are low-grade gliomas (I-II) and high-grade gliomas (III-IV). Low-grade gliomas tend to grow slowly and can be either diffuse or more localized. High-grade gliomas grow at a rapid pace, are undifferentiated and have a worse prognosis than low-grade gliomas. Seventy percent of grade II gliomas transform into grade III and IV tumors within 5–10 years after initial diagnosis and then behave clinically like the higher-grade tumors (Maher, 2001).

The diagnosis of a malignant brain tumor is associated with a low cure rate and a short survival as the illness progresses and therefore has a tremendous impact on patients' lives. However, in the last decades treatment of primary brain tumors has improved considerably with the refinement of surgical procedures, chemotherapy, radiation and the development of new techniques such as gene therapy (Giordana & Clara, 2006). As a result, life-expectancy is improved and patients live longer than ever with the disease and its neurological consequences (Barnholtz-Sloan, Sloan & Schwartz, 2003). Common neurological deficits associated with brain tumors are hemi- and tetraparesis (78% of the patients with a primary brain tumor) visual-perceptual deficits (53%), sensory loss (38%) and bowel and bladder dysfunction. Other neurological deficits include cranial nerve palsies, dysarthria, dysphagia and ataxia. In addition, approximately 80% of patients with primary brain tumors have cognitive impairments (Mukand et al., 2001). The severity of functional deficits depends on the type and location of the tumor and the age of the patient. Older patients more often have additional medical conditions, while in younger patients physical limitations are more often combined with financial and marital problems (Mackworth, Fobair &

Prados, 1992; Giordana & Clara, 2006). Apart from the neurological deficits mentioned, patients with brain tumors often suffer from fatigue and depression as a result of the illness and medical treatment.

Fatigue and somnolence are described as being common in patients with brain tumors. For example, detailed observations of 19 brain tumor patients led to identification of a somnolence syndrome that follows treatment (Faithful & Brada, 1998). The most commonly reported symptoms are excessive drowsiness, lethargy, perceived clumsiness, having difficulty concentrating and being mentally slow. Eighty percent of brain tumor patients treated with radiation therapy experience symptoms of fatigue and 40% of long-term survivors remain extremely fatigued (Lovely, 1999; Struik et al., 2008).

With regard to cognition, a large proportion of patients with primary brain tumors have impairments, as was mentioned earlier (Mukand et al., 2001). This can be caused by the tumor itself or it can be the result of the received medical treatment (e.g. radiotherapy, surgery or medication) (Taphoorn & Klein, 2004). The cognitive impairment may be caused by cerebral cortical lesions but, because of the widespread cortical-subcortical connections, may also result from subcortical white-matter disease or even from damage to cerebellar structures (Taphoorn & Klein, 2004). Glioma patients with tumors in the dominant hemisphere have more cognitive deficits than patients with a tumor in the non-dominant hemisphere. Impairments occur in various cognitive domains, particularly in attention and concentration, memory and executive functions (Taphoorn & Klein, 2004). Objective cognitive test results do not necessarily reflect the patient's cognitive complaints (Janda et al., 2007). Cognitive complaints can also be caused by fatigue rather than impaired cognitive ability (Taphoorn & Klein, 2004). In addition, cognitive changes can be amplified by comorbid psychosocial problems, such as reactive depression (Giordana & Clara, 2006). Patients with depressed mood may underestimate their cognitive functioning and cognitive complaints might indicate feelings of anxiety or depression (Hermelink et al., 2010).

Depressive symptoms are reported by a significant proportion of patients with primary brain tumors (Rooney, Carson & Grant, 2010). Particular types of tumors are more closely related to depression than others. Among patients with meningiomas, high-grade gliomas and pituitary tumors the estimated incidence is higher than in patients with other types of brain tumors (Wefel, Armstrong & Kohli, 2011). In patients with cancer, those diagnosed with glioma appear to have the highest risk of developing psychiatric complications in the period surrounding the diagnosis.

The prevalence of depressive symptoms in glioma patients as assessed by clinician-rated measures is estimated between 6 and 28% (Rooney, Carson & Grant, 2011). Primary symptoms of depression are difficult to distinguish from the consequences of tumor or treatment (Rooney, Carson & Grant, 2010). For example, radiation therapy and chemotherapy could potentially cause depressive symptoms, and high-dose corticosteroids are known to result in behavioral changes and labile affect (Pelletier et al., 2002). The brain tumor itself can also be a cause of depression, due to alterations in cortical-limbic pathways (Wefel, Armstrong & Kohli, 2011). Despite the cause, true clinical depression can develop following a decline in health and is of great practical relevance to patients. Many patients experience feelings of loss of control, hopelessness, relationship-related concerns and anxiety in reaction to the diagnosis and possible death (Pelletier et al., 2002). They experience immense stress as they try to make sense of, and find meaning in their changed life situation.

The aforementioned consequences of brain tumors and their treatment pose serious threats to the quality of life (QOL) of these patients (Liu et al., 2009). QOL is a concept that encompasses the multidimensional well-being of a person and reflects an individual's overall satisfaction with life. QOL is a broad term that involves several dimensions, including physical and functional status, as well as emotional and social well-being. Among patients with brain tumors, the overall symptom burden and disability is high, particularly in recurrent disease (Liu et al., 2009). In one study, 45% of patients with low-grade glioma reported low overall QOL. The study showed that although nearly all patients were capable of self-care, less than half were able to carry out normal activities without any restriction (Gustafsson, Edvardsson & Ahlstrom, 2006). For glioma patients in general, QOL is influenced by both tumor- and non-tumor-related factors. QOL appears to be most affected by the extent of tumor involvement, treatment status, performance status, gender, marital status, and whether or not patients are able to work (Weitzner et al., 1996).
Cognitive deficits and symptoms of fatigue and depression are related to a low QOL. Results from the mentioned study from Gustafsson, Edvardsson &Ahlstrom (2006) showed that of all variables tested, fatigue has the strongest relationship with overall QOL in patients with a low-grade glioma. Additionally, for patients with a primary brain tumor in general, cognitive deficits and symptoms of depression are associated with a decrease of their QOL (Janda et al., 2007).

Although fatigue, cognitive deficits and depression are often overlooked symptoms, there are several treatment options such as cognitive behavioral therapy or pharmacological interventions. An example of the latter is the treatment with a traditional psychostimulant such as methylphenidate or with a newer kind of psychostimulant such as modafinil. Methylphenidate has proved to be effective to treat depression, cognition and fatigue in several patient populations (Berridge & Devilbiss, 2011; Auriel, Hausdorff & Giladi, 2009; Siddall, 2005). A disadvantage of using this drug is its short half life which requires the patient to take two to three dosages a day (Pharmacotherapeutical Compass, 2012). Modafinil is considered a good alternative to methylphenidate. This drug was developed in France in the early 1990s as a wakefulness and alertness-enhancing drug (Gehring et al., 2011; Ballon & Feifel, 2006). There is a lack of consensus in scientific literature about the precise neurochemical mechanism of action. It was originally thought that modafinil, in contrast to other psychostimulants, had a nondopamine mechanism. However, recent studies have provided evidence for the participation of dopamine and norepinephrine (Minzenberg & Carter, 2008). The most recent research findings suggest that modafinil increases dopamine in the striatum and norepinephrine in the hypothalamus and thalamus (Minzenberg & Carter, 2008). In addition, modafinil inhibits GABA release and activates glutamatergic effects (Ferraro et al., 1999; Young, 2012). Modafinil belongs to a class of drugs called eugeroics (meaning "good arousal") (Kohli et al., 2009; Pharmacotherapeutic Compass, 2012). The drug does not disturb sleep, its uniqueness lies in the fact that it only seems to cause wakefulness when vigilance is sought by the person to whom the drug was administered (Wolpe, 2002). As a result, the highs and lows associated with other psychostimulants, such as amphetamines, are absent in eugeroics. Other benefits of modafinil compared with traditional psychostimulants are that modafinil is less likely to cause significant side effects and that it has a low dependency potential (Rugino & Copley, 2001).

Modafinil was first marketed as a treatment for the excessive somnolence as a feature of narcolepsy (Minzenberg & Carter, 2008; Ballon & Feifel, 2008). In a study in patients with Multiple Sclerosis, use of modafinil appeared to significantly reduce symptoms of fatigue (Brown, Howard & Kemp, 2010). The drug also appears to influence cancer-related fatigue (Blackhall et al., 2009).

Alongside fatigue, modafinil has been found to be effective in enhancing cognitive functioning in healthy people and in patients with a number of medical and psychiatric conditions such as Attention Deficit Hyperactivity Disorder (ADHD) and depression (Rugino & Copley, 2001;

Minzenberg & Carter, 2008). The drug also appears to improve cognitive performance in breast cancer survivors treated with chemotherapy (Kohli et al., 2009). Patients treated with modafinil showed improvement in attention and were better at storing, retaining, and retrieving both verbal and visual information.

With regard to the effect of modafinil on depression, some research is done. Modafinil appears to be a good addition to SSRI treatment in patients with a mood disorder (Ninan et al., 2004). The drug also seems effective in patients with cancer and depressive symptoms (Blackhall et al., 2009). When cancer patients were given modafinil, scores on a depression scale declined within two weeks, indicating a significant decrease in depressive symptoms.

Lastly, modafinil appears to have a beneficial effect on the overall QOL, as evidenced by studies in patients with Multiple Sclerosis (Brown, Howard & Kemp, 2010) and cancer (Blackhall et al., 2009).

Despite the studies described above, indicating positive effects of modafinil on fatigue, cognition, mood and QOL, very little is known about its effects on similar symptoms in patients with primary brain tumors. A pilot study has been performed to investigate the effect of modafinil on cognitive function, mood, fatigue levels and QOL in brain tumor patients, but results have not been published (Kaleita et al., 2006). In a different pilot study examining the effects of methylphenidate and modafinil on cognitive functioning, fatigue, sleep disturbance, mood and QOL, modafinil had a significant positive effect on processing speed and executive function requiring divided attention in patients with a primary brain tumor (Gehring et al., 2012). Evidence of a general beneficial effect on patient-reported measures of fatigue, mood and QOL was found as well.

The present study builds on these previous studies, taking earlier limitations into account. To rule out non-specific treatment effects, a double-blind placebo controlled crossover study design will be used. The purpose of the present trial is to investigate the effect of modafinil on fatigue, cognitive functioning, depression and overall QOL. It is hypothesized that modafinil will have a positive effect on all four of these outcome measures in patients with a primary brain tumor. Alleviation of these (neuro)psychological symptoms could significantly improve patients' emotional and physical well-being and their day-to-day functioning.

Methods

Participants

Patients were recruited at three tertiary referral centers for brain tumor patients: the VU University Medical Center and the Academic Medical Center (both situated in Amsterdam, the Netherlands) and the Medical Center Haaglanden (in the Hague, the Netherlands). Patients were included in the study if 1) heightened experience of fatigue was reported (score >27 on the Checklist Individual Strength (CIS, Vercoulen et al., 1999)), 2) a primary brain tumor (i.e. a low- or high-grade glioma or meningioma) was histologically confirmed, 3) there were no signs of tumor recurrence in the last six months and 4) they had signed a written informed consent form. Patients were excluded if they had 1) a history of psychiatric disease or symptoms, 2) insufficient mastery of the Dutch language and/or 3) were inable to communicate adequately.

Outcome measures

Fatigue

The *Checklist Individual Strength (CIS)* was used to measure fatigue (Vercoulen et al., 1999). The CIS is a multidimensional fatigue scale; it measures four aspects of fatigue during the previous two weeks. These four aspects are: fatigue severity, concentration problems, reduced motivation and reduced activity. Each item is scored on a seven-point Likert scale. Total scores on every subscale were obtained by adding the individual items, with high scores indicating a high level of fatigue, a high level of concentration problems, low motivation and a low activity level. A score between 27 and 35 indicated a heightened experience of fatigue and is based on scores of healthy controls.

Cognitive functioning

To measure cognitive functioning a standardized neuropsychological test battery was used. The test battery consisted of a wide range of tests to cover several cognitive domains. The *Rey Auditory Verbal Learning Test (AVLT*, Dutch version) was used to measure various aspects of verbal learning and recall (Rey, 1941). The AVLT requires patients to memorize a list of 15 verbally presented items five consecutive times and reproduce them. After a 20-minute delay, the patient is asked to reproduce the 15 items again (delayed recall) and to identify the same 15 items from a list of 30 words (recognition). At each assessment moment different versions of the test were used to prevent a learning effect. The measures used for analysis are memory performance on trial 1 as an indication of immediate recall, total recall after five trials, delayed recall and recognition after 20 minutes as indicators of memory consolidation into long-term memory and a

delta score as a measure of learning capacity.

The *Concept Shifting Test* was used here to measure functions associated with executive functioning and mental speed. In all conditions, patients were given sheets of paper with sixteen circles to be crossed out as fast as possible. In part A, patients were asked to cross out randomly distributed digits (1 to 16) in the circles in ascending order. In part B, patients crossed out 16 letters (A to P) in alphabetical order instead, and in part C, patients were instructed to alternate between letters and digits (1-A, 2-B etc.) Finally, the motor component of this task was measured by three dummy conditions in which empty circles have to be crossed out as fast as possible, requiring no neurocognitive capacity except for graphomotor speed (Van der Elst et al., 2006a).

The *Memory Comparison Test* was used here to examine working memory (Brand & Jolles, 1987; Sternberg, 1975). In the test, patients were shown a sheet of paper that depicts a set of one to four letters. This sheet was replaced after 5 seconds by a test sheet that contains a matrix of 120 letters. Patients were instructed to cross out the letters that were in the set that was shown before (Van der Elst, 2007).

To measure attentional functioning and information processing, the pen-and-paper version of the *Letter Digit Substitution Test (LDST)* was used (Van der Elst et al., 2006b). The patients were given a sheet of paper with a code indicating 9 symbols corresponding to 9 digits. By looking up the corresponding digit, participants had to match as many symbols and digits as possible within 90 seconds.

The *Categorical Word Fluency Test* was used here to measure executive functioning (cognitive flexibility). This is a subtest of the Groninger Intelligentie Test (GIT; Luteijn & Ploeg, 1983). The test requires patients to generate words from a specific semantic category, in this case animals, in a 1-minute period.

To assess attention, the *Stroop Colour-Word Test* was administered (Stroop, 1935; Dutch version Hammes, 1971). Patients were shown three different cards. The first two cards required reading aloud color names and naming colors. The third card is the interference card which consists of color names, printed either in the denoted color (e.g. ‘RED’ printed in red ink) or in a different color (e.g. ‘RED’ printed in green ink). Participants were asked to name the inkcolor outloud and not the written word. The difference between the time on card three (color–word card) and the

time on card two (color card) is chosen to represent interference.

Subjective cognitive functioning was assessed with the *Medical Outcome Study (MOS) subjective cognitive functioning scale* (Stewart & Ware, 1992; Taphoorn et al., 2010). This 6-item scale assesses day-to-day problems in cognitive functioning including difficulty with reasoning and problem solving, slowed reaction time, forgetfulness, and problems with concentration (range 1-6). Raw scores are converted linearly to a 0 to 100 scale, with higher scores indicating higher levels of self-reported cognitive functioning.

Depression

The *Center for Epidemiologic Studies Depression Scale (CES-D)* (Radloff, 1977; Bouma et al., 1995) was used to measure symptoms of depression. This survey consists of 20 statements. Participants indicate on a 4-point scale how often they feel a statement was applicable to their situation during the last week. Scores range between 0-60, with higher scores indicating more feelings of depression. In the general population, respondents with a total score of 16 or higher are considered depressed. The CES-D has 4 separate factors: depressive affect, somatic symptoms, positive affect, and interpersonal relations.

Quality of life

Quality of life was assessed with the *Short-Form Health Survey (SF-36)* (Ware & Sherbourne, 1992). This self-report questionnaire is composed of 36 items, organized into 8 multi-item scales assessing physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. The SF-36 also yields two higher order component scores, one for Physical Health (Physical Component Score, PCS) and one for Mental Health (Mental Component Score, MCS).

Neurological functioning

The 20-item *Brain Cancer Module (BN20)* (Osaba et al., 1996; Taphoorn et al., 2010) was used to assess neurological functioning. It contains 4 multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items asking about headaches, seizures, drowsiness, hair loss, itching, weakness in the legs, and difficulties with bladder control. The BN20 raw scores were converted to scales ranging from 0 to 100, with higher scores representing lower levels of functioning.

Procedure

Participants were randomized into two groups. Patients, treating physicians and researchers were blind to treatment allocation. Both groups would first receive six weeks of treatment with either placebo or modafinil. This was followed by a washout period of one week, where all possible effects of the medication disappeared. Hereafter, another treatment period of six weeks took place, in which groups received placebo or modafinil (the opposite of the first treatment). All patients were therefore treated with both modafinil and placebo. Treatment began with 100 mg modafinil or matching placebo, upon waking and at lunch (200 mg/day in total). After one week, the dose was doubled (400 mg in total). If participants experienced adverse events at the higher dose, they would be allowed to decrease the medication to the previous dose after consulting the physician involved in the trial. Patients continued at either 200 mg or 400 mg a day until the second visit, six weeks after the initial visit.

Assessments took place at baseline (T1), immediately after the first treatment with either placebo or modafinil (after six weeks; T2) and immediately after the second treatment with either placebo or modafinil (after twelve weeks; T3). Clinical data (including year of diagnosis, type of tumor and received anti-tumor treatment) were obtained at baseline. At all assessments physical examination was carried out by a physician. If patients appeared to have drug side-effects, they were advized by the physician to lower the dose of the medication or to stop participating in the trial. The examination included a general assessment of physical functioning (blood pressure, condition of heart and lungs, and condition of skin) and a neurological examination (higher cortical functions, cranial nerves, motor examination, sensory examination, reflexes and coordination). At T2 and T3 a patient history was documented. Patients were asked about differences in fatigue and neuro-oncological complaints, seizures and possible side effects of medication.

Statistical analysis

Statistical analysis was performed with SPSS software, version 20 (SPSS Inc., 2011). Cognitive testscores were converted to z-scores, using the means and standard deviations of the scores of the patients at baseline. In order to accomplish data reduction, summary measures were calculated to detect possible deficits in the cognitive domains of 1) verbal memory, 2) working memory, 3) attentional functioning, 4) information processing, 5) executive functioning and 6) psychomotor functioning. The neuropsychological tests corresponding to these domains are shown in Table 1. Construction of these cognitive domains has previously been reported and was based on a

principal component analysis (PCA) using Varimax rotation with Kaiser nomalization (Wessels et al., 2007). Standard scoring rules were used to convert the data from the questionnaires. Mean imputation was used to handle missing values. To test whether the outcome measures were normally distributed, Kolmogorov-Smirnov tests were used. Since none of the outcome measures were normally distributed, Wilcoxon signed-rank tests were used to determine differences within patients in fatigue, cognition, depression and QOL. Given the small sample size, no corrections for multiple statistical testing were applied. An alpha level of ≤ 0.05 was considered statistically significant, an alpha level of ≤ 0.10 was considered a trend. Additionally, a possible effect of modafinil on neurological functioning was also examined.

It can be expected that patients who have little to no complaints or deficits regarding fatigue, depression, cognitive functioning and QOL at baseline measure, also won't experience an effect when treated with modafinil or placebo. Within the group of participants, these patients will 'balance out' the group of patients who had psychological complaints and cognitive deficits at baseline. Thus, the participant group was additionally split based on all baseline test scores. When new groups were formed, Wilcoxon signed-rank tests were again used to determine statistical significance of differences.

Table 1. Neuropsychological tests and corresponding cognitive domains

Cognitive domain	***Neuropsychological test***
Verbal memory	Auditory Verbal Learning Test
Working memory	Memory Comparison Test
Attentional functioning	Stroop Colour-Word Test
Information processing	Letter Digit Substitution Test
Executive functioning	Concept Shifting Test
	Categorical Word Fluency Test
Psychomotor functioning	Concept Shifting Test
	Letter Digit Substitution Test

Results

Sample characteristics

Participants were recruited from March 2009 until January 2012. A total of 392 patients with a brain tumor were invited for screening, forty-one of them met the inclusion criteria and signed the informed consent. Thirty-seven patients were randomly assigned to a treatment arm, whereas 4 patients dropped out before randomization. Twenty-four patients received modafinil first, thirteen patients received the placebo first. Ten patients subsequently dropped out. Reasons for dropping out were discontinued medication due to side effects (7), epileptic seizures (1), back pain(1) and missed follow-up (1). Figure 1 shows details of the recruitment phase and the participant flow.

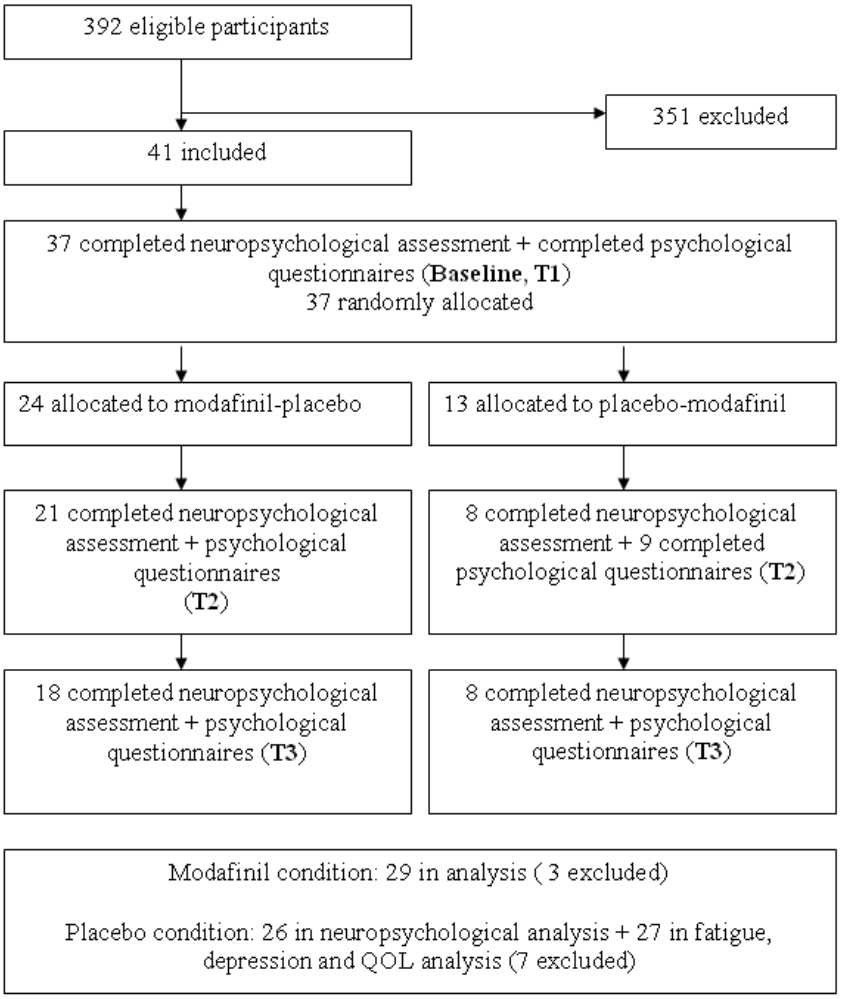

Figure 1. A participant flow diagram

Table 2 presents the clinical and demographic profile of the participants. The mean age of the patients was 42.16 years. More women participated than men (62.2% vs. 37.8%). With respect to

neuro-oncological characteristics, most participants had a low-grade glioma (37.8%) and mean time since diagnosis was 49.46 months.

Table 2. Demographic and clinical characteristics of sample

		Participant group (*N*= 37)
Age in years *M* (SD)		48.16 (12.02)
Gender *N* (%)		
	Male	14 (37.8%)
	Female	23 (62.2%)
Educational level *N (%)*		
	Low	10 (27%)
	Medium	15 (40.5%)
	High	11 (29.7)
Tumor grade *N* (%)		
	Grade I	15 (40.5%)
	Grade II	10 (27.0%)
	Grade III	7 (18.9%)
	Grade IV	5 (13.5%)
Tumor type		
	Meningioma	12 (32.4%)
	Low-grade glioma	14 (37.8%)
	High-grade glioma	11 (29.7%)
Tumor location *N* (%)		
	Frontal	13 (35.1%)
	Temporal	5 (13.5%)
	Parietal	6 (16.2%)
	Occipital	2 (5.4%)
	Mixed	6 (16.2%)
	Other	5 (13.5%)
Tumor lateralisation *N* (%)		
	Left	15 (40.5%)
	Right	20 (54.1%)
	Bilateral	2 (5.4%)
Epilepsy *N* (%)		
	Yes	12 (32.4%)
	No	25 (67.6%)

Neurosurgical intervention *N* (%)		
	Resection	33 (89.2%)
	Biopsy	2 (5.4%)
	None	2 (5.4%)
Months since time of diagnosis *M* (range)		49.46 (16-197)
	< 36 months *N*(%)	18 (48,6%)
	> 36 months *N*(%)	19 (51,4%)
Progressive disease during intervention *N* (%)		
	Yes	2 (5,4%)
	No	37 (94,6%)

Fatigue

Regarding fatigue, total CIS-scores were significantly lower when the modafinil condition and the placebo condition were compared to baseline measure (M= 81.00, sd= 26.73, p= .003 and M= 82.07, sd= 28.56, p= .001, respectively). The results are shown in Table 3 and 4). However, no significant difference was found between the two treatment conditions. This indicates that patients experienced equal decrease in fatigue in both the modafinil and the placebo condition. The same was found for the subscales 'Concentration problems' and 'Reduced activity'; in both the modafinil condition (M= 26.48, sd= 14,48, p< .001 and M= 12.85, sd= 5.90, p= .003, respectively) and the placebo condition (M= 27.56, sd= 13.02, p< .001 and M= 12.93, sd= 5.48, p< .001, respectively) scores were lower compared to baseline, but they did not differ from each other. For the subscale 'Reduced motivation', only the score in the placebo condition was significantly lower compared to baseline, although a trend was noticed between baseline and the modafinil condition (M= 18.25, sd= 7.94, p= .040 and M= 16.72, sd= 7.13, p= .094, respectively). For the 'Fatigue severity' scale, only a significant difference was found between baseline and the modafinil condition (M= 25.08, sd= 13.64, p= .004).

For the total score on the CIS the group of patients was split in those who scored higher or lower than 83 (based on normative data from Vercoulen et al., 1999). Analyses of both the higher and lower scoring groups did not yield different results than described above (data not shown).

Table 3. Descriptive statistics of the CIS on baseline measure and the modafinil and placebo condition.

	Baseline		Modafinil		Placebo	
Measure	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Concentration problems	42.35 (6.64)	29	26.48(14.48)	25	27.56 (13.02)	28
Reduced motivation	20.69 (9.72)	29	16.72 (7.13)	25	18.25 (7.94)	28
Reduced activity	16.90 (5.46)	29	12.85 (5.90)	26	12.93 (5.48)	28
Fatigue severity	16.03 (8.94)	25	25.08 (13.64)	28	21.57 (14.18)	29
Total score	95.97 (19.77)	29	81.00 (26.73)	25	82.07 (28.56)	28

Table 4. Analysis of the CIS comparing baseline measure and the modafinil and placebo condition.

Measure		*Z*	*P*
Concentration problems	Baseline -Modafinil	-3.92	<.001*
	Baseline - Placebo	-4.17	<.001*
	Modafinil - Placebo	-0.55	.581
Reduced motivation	Baseline -Modafinil	-1.67	.094
	Baseline - Placebo	-2.05	.040*
	Modafinil - Placebo	-0.88	.381
Reduced activity	Baseline -Modafinil	-3.01	.003*
	Baseline - Placebo	-3.49	<.001*
	Modafinil - Placebo	-0.51	.614
Fatigue severity	Baseline -Modafinil	-2.85	.004*
	Baseline - Placebo	-1.38	.167
	Modafinil - Placebo	-1.00	.319
Total score	Baseline -Modafinil	-3.00	.003*
	Baseline - Placebo	-3.18	.001*
	Modafinil - Placebo	-0.36	.716

* $p < .05$

Cognition

Objective cognitive functioning

With respect to cognition, the scores for the domain 'Working memory' were higher in the modafinil condition when compared to baseline and a trend was show when modafinil was compared to the placebo condition (M= -0.33, sd= 1.14, *p*=.023 and M= 0.22, sd= 0.97, *p*= .072 respectively; see Table 5 and 6). This indicates that patients in the modafinil condition showed better working memory. On the cognitive domains 'Attentional functioning' and 'Psychomotor control', the scores in the placebo condition were higher compared with baseline (M= -0.01, sd= 0.98, *p*=.025 and M=0.20, sd= 0.49, *p*= .034, respectively), but not with modafinil. In the domains of 'Verbal memory', 'Information processing' and 'Executive functioning' and for overall cognition, no significant differences were found.

For cognition, the group of patients was split in a group that had a z-score ≤ 0 on three or more cognitive domains and a group that did not (see Table 7 and 8). The findings for the overall cognition score did not differ from the results of the whole group. However, for the group that had a z-score ≤ 0 on three or more cognitive domains at baseline, the results on several cognitive domains were different. For this group, higher scores on the cognitive domains 'Executive functioning' (M= .23, sd= 0.83, *p*= .023 and M= .01, sd= 1.11, *p*=.053, respectively), 'Working memory'(M= .13, sd= 0.90, *p*= .009 and M=.01, sd= 1.14, *p*= .044, respectively) and 'Psychomotor functioning' (M= .23, sd= 0.42, *p*= .023 and M= 3.83, sd= 14.14, *p*= .008, respectively) were found in the modafinil and placebo condition when compared to baseline measure. This indicates patients showed better executive functioning, working memory and information processing speed in both of the conditions. No difference was found between the modafinil and placebo conditions. In the domain 'Information processing', the scores in the modafinil and placebo condition were also higher when compared to baseline measure (M= -.02, sd= 0.87, *p*=.039 and M= 2.88, sd= 9.33, *p*= .005, respectively). In this case both conditions differed from each other, with the scores being higher for the placebo group (*p*= .016). With regard to 'Verbal memory' and 'Attentional functioning', the score in the placebo condition was higher when compared to baseline and the modafinil condition (M= -.41, sd= 0.63, *p*= .020 and M= 0.19, sd= 0.70, *p*= .033, respectively). In the domain 'Attentional functioning', the score in the placebo group was higher when compared to baseline, but not when compared to the modafinil group (M= -.84, sd= 1.47, *p*= .001, respectively. For the group that did not have a z-score ≤ 0 on three or more cognitive domains the findings did not differ from the results of the whole group.

Table 5. Descriptive statistics of neuropsychological tests on baseline measure and the modafinil and placebo condition

Measure	Baseline		Modafinil		Placebo	
	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Verbal memory domain	-0.08 (0.72)	29	0.01 (0.86)	26	0.09 (0.96)	27
Working memory domain	-0.33 (1.14)	29	0.29 (0.81)	26	0.22 (0.97)	27
Attentional functioning domain	-0.20 (1.39)	29	-0.01 (0.98)	26	0.42 (0.59)	27
Information processing domain	-0.04 (1.02)	28	0.24 (1.09)	25	1.90 (7.23)	27
Executive functioning domain	-0.15 (0.80)	29	0.23 (0.74)	26	0.10 (0.98)	26
Psycho-motor functioning domain	0.03 (0.64)	28	0.20 (0.49)	25	2.44 (10.88)	27
Overall cognition	-0.11 (.66)	29	0.14 (0.66)	28	0.39 (1.40)	28

Table 6. Analysis of the neuropsychological tests comparing baseline measure and the modafinil and placebo condition.

Measure		*Z*	*P*
Verbal memory	Baseline -Modafinil	-0.72	.469
	Baseline - Placebo	-1.63	.102
	Modafinil - Placebo	-1.40	.162
Working memory	Baseline -Modafinil	-2.27	.023*
	Baseline - Placebo	-1.80	.072
	Modafinil - Placebo	-0.26	.797
Attentional functioning	Baseline -Modafinil	-0.01	.990
	Baseline - Placebo	-2.23	.025*
	Modafinil - Placebo	-1.71	.086
Information processing	Baseline -Modafinil	-0.91	.361
	Baseline - Placebo	-1.66	.096
	Modafinil - Placebo	-1.58	.114
Executive functioning	Baseline -Modafinil	-1.26	.209
	Baseline - Placebo	-0.88	.381
	Modafinil - Placebo	-0.31	.753
Psychomotor functioning	Baseline -Modafinil	-0.60	.549
	Baseline - Placebo	-2.12	.034*
	Modafinil - Placebo	-1.01	.316
Overall cognition	Baseline -Modafinil	-1.32	.187
	Baseline - Placebo	-1.48	.139
	Modafinil - Placebo	-0.63	.532

* $p < .05$

Table 7. Descriptive statistics of neuropsychological tests on baseline measure and the modafinil and placebo condition for patients with z<0 on three or more cognitive domains at baseline.

	Baseline		Modafinil		Placebo	
Measure	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Verbal memory domain	-0.41 (0.63)	17	-0.31 (0.79)	15	0.19 (0.70)	16
Working memory domain	-.90 (1.10)	17	0.13 (0.90)	15	0.01 (1.14)	16
Attentional functioning domain	-0.84 (1.47)	17	-0.27 (1.11)	15	0.37 (0.65)	16
Information processing domain	-0.68 (0.52)	16	-0.02 (.87)	14	2.88 (9.33)	16
Executive functioning domain	-0.57 (0.64)	17	0.23 (0.83)	15	0.01 (1.11)	15
Psycho-motor functioning domain	-0.34 (0.52)	16	0.23 (0.42)	14	3.83(14.14)	16
Overall cognition	-0.53 (0.48)	17	0.12 (0.65)	16	0.47 (1.82)	16

Table 8. Analysis of neuropsychological tests comparing baseline measure, modafinil and placebo for patients with z<0 on three or more cognitive domains at baseline.

Measure		*Z*	*P*
Verbal memory	Baseline -Modafinil	-1.53	.125
	Baseline - Placebo	-2.33	.020*
	Modafinil - Placebo	-2.13	.033*
Working memory	Baseline -Modafinil	-2.61	.009*
	Baseline - Placebo	-2.02	.044*
	Modafinil - Placebo	-0.53	.594
Attentional functioning	Baseline -Modafinil	-1.02	.307
	Baseline - Placebo	-3.21	.001*
	Modafinil - Placebo	-1.41	.158
Information processing	Baseline -Modafinil	-2.06	.039*
speed	Baseline - Placebo	-2.84	.005*
	Modafinil - Placebo	-2.41	.016*
Executive functioning	Baseline -Modafinil	-2.27	.023*
	Baseline - Placebo	-1.93	.053*
	Modafinil - Placebo	-0.66	.510
Psychomotor functioning	Baseline -Modafinil	-2.27	.023*
	Baseline – Placebo	-2.67	.008*
	Modafinil – Placebo	-.734	.463
Overall cognition	Baseline –Modafinil	-2.38	.017*
	Baseline – Placebo	-2.59	.010*
	Modafinil – Placebo	-0.51	.609

* $p < .05$

Subjective cognitive functioning

In addition to objective cognitive functioning, the effect of modafinil on subjective self-reported cognitive functioning was examined (see Table 9 and 10). On the MOS-subscale 'Sustained attention' the scores were lower in the modafinil condition than at baseline (M= 2.67, sd= 1.07, *p*=.043), an effect that is not found for the placebo condition. This suggests that patients in the modafinil condition reported less sustained attention. On the subscales 'Problem solving' and 'Concentration' the scores in both the modafinil condition (M= 2.38, sd= 1.39, *p*=.014. and M= 2.69, sd= 1.44, *p*= .014, respectively) and the placebo condition (M= -2.47, sd= 1.53, *p*= .020. and M= 2.70, sd= 1.47, *p*= .012, respectively) were lower than at baseline, but no difference between the conditions was found. This indicates patients in both conditions had more problems in day-to-day cognitive functioning than they had at baseline measure. For the other subschales, no other differences were found.

Depression

With respect to depression, scores on the 'Somatic retarded activity'-subscale were lower in both the modafinil and the placebo condition compared to baseline (M= 5.96, sd= 4.01, *p*= .040 and M= 5.38, sd= 3.63, *p*= .023, respectively). The results are shown in Table 11 and Table 12. This suggests that patients in both conditions showed less somatic retarded activity. No other differences were found.

Here, the group was split at a score of 16, since this is the cutoff score normally used as an indication for depression (Radloff, 1977; Bouma et al., 1995). This did not result in different findings.

Table 9. Descriptive statistics of the MOS on baseline measure and the modafinil and placebo condition.

	Baseline		Modafinil		Placebo	
Measure	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Problem solving	3.10 (1.42)	30	2.38 (1.39)	26	2.47 (1.53)	30
Concentration	3.40 (1.38)	30	2.69 (1.44)	26	2.70 (1.47)	30
Confusion	2.40 (1.25)	30	2.33 (1.41)	27	2.13 (1.20)	30
Forgetfulness	2.97 (1.19)	30	2.71 (1.12)	28	2.70 (1.32)	30
Sustained attention	3.23 (1.36)	30	2.67 (1.07)	27	2.87 (1.36)	30
Slowness	2.63 (1.30)	30	2.50 (1.24)	26	2.40 (1.25)	30
Cognitive complaints	32.59 (18.54)	30	28.70(16.50)	24	28.64 (21.14)	28

Table 10. Analysis of the MOS comparing baseline measure and the modafinil and placebo condition.

Measure		*Z*	*P*
Problem solving	Baseline -Modafinil	-2.46	.014*
	Baseline - Placebo	-2.33	.020*
	Modafinil - Placebo	-0.21	.833
Concentration	Baseline -Modafinil	-2.45	.014*
	Baseline - Placebo	-2.52	.012*
	Modafinil - Placebo	-0.71	.480
Confusion	Baseline -Modafinil	-0.15	.883
	Baseline - Placebo	-1.21	.228
	Modafinil - Placebo	-0.95	.343
Forgetfulness	Baseline -Modafinil	-1.27	.205
	Baseline - Placebo	-1.38	.169
	Modafinil - Placebo	-0.18	.861
Sustained attention	Baseline -Modafinil	-2.02	.043*
	Baseline - Placebo	-1.64	.102
	Modafinil - Placebo	-0.05	.957
Slowness	Baseline -Modafinil	-0.74	.458
	Baseline - Placebo	-0.99	.321
	Modafinil - Placebo	-1.01	.314
Cognitive complaints	Baseline -Modafinil	-0.59	.558
	Baseline - Placebo	-2.13	.033*
	Modafinil - Placebo	-0.87	.385

* $p < .05$

Table 11. Descriptive statistics of the CES-D on baseline measure and the modafinil and placebo condition.

	Baseline		Modafinil		Placebo	
Measure	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Somatic retarded activity	7.10 (3.19)	29	5.96 (4.01)	23	5.38 (3.63)	29
Depressed affect	3.30 (2.87)	30	2.62 (2.48)	24	2.76 (2.96)	29
Positive affect	4.27 (3.21)	30	4.00 (3.04)	25	4.21 (3.79)	29
Interpersonal affect	0.63 (1.03)	30	.80 (1.22)	25	0.52 (1.15)	29
Total Score	14.97 (9.01)	29	14.22 (9.29)	23	13.36 (9.43)	28

Table 12. Analysis of the CES-D comparing baseline measure and the modafinil and placebo condition.

Measure		*Z*	*P*
Somatic retarded activity	Baseline -Modafinil	-2.06	.040*
	Baseline - Placebo	-2.27	.023*
	Modafinil - Placebo	-0.75	.454
Depressed affect	Baseline -Modafinil	-0.57	.567
	Baseline - Placebo	-0.80	.426
	Modafinil - Placebo	-0.54	.587
Positive affect	Baseline -Modafinil	-0.14	.888
	Baseline - Placebo	-0.21	.832
	Modafinil - Placebo	-0.36	.721
Interpersonal affect	Baseline -Modafinil	-0.24	.808
	Baseline - Placebo	-0.31	.756
	Modafinil - Placebo	-1.55	.121
Total Score	Baseline -Modafinil	-0.65	.948
	Baseline - Placebo	-1.59	.111
	Modafinil - Placebo	-0.73	.466

* $p < .05$

Quality of Life

On the total 'PCS'-scale and on the subscales 'Role limitations due to physical health', 'Physical functioning', and 'Vitality' we found significantly higher scores in both the modafinil condition and the placebo condition when compared to baseline measure (M= 45.91, sd= 7.93, *p*= .001 and M= 44.87, sd= 9.28, *p*=.004, respectively for the 'PCS'- scale; M= 49.00, sd= 44.18, *p*= .005 and M= 47.12, sd= 39.55, *p*= .001, respectively for 'Role limitations due to physical health', M= 77.29, sd= 20.89, *p*= .023 and M= 76.72, sd= 24.03, *p*=.042, respectively for the 'Physical functioning' and M= 51.94, sd= 18.08, *p*= .014 and M= 53.45, sd= 15.01, *p*= .002, respectively for 'Vitality'). Results are shown in Tables 13 and 14. These results indicate that patients in both conditions reported less role limitations due to physical health as well as better physical health and vitality. No other differences were found.

Additionally, the group of patients was split at a score of 40 on the PCS and MCS scales. The findings for the split groups did not differ from the results of the whole group.

Neurological functioning

On the BN-20, the scores on the subscales 'Visual disorder' and 'Drowsiness' were lower in both the modafinil and the placebo condition compared to baseline (M= 24.36, sd= 27.58, *p*<.001 and M= 28.74, sd= 31.78, *p*=.005, respectively for 'Drowsiness' and M= 12.89, sd= 13.49, *p*= .017 and M= 12.70, sd= 14.41, *p*= .002, respectively for 'Visual disorder') (see tables 15 and 16). This indicates that on these two subscales, patients showed better functioning in both conditions. On the subscale 'Bothered by itching skin' the scores were lower in the modafinil condition when compared to the placebo condition and baseline measure (M= 11.11, sd= 20.67, *p*=.021). On the other hand, on the subscale 'Motor dysfunction' the scores were lower in the placebo condition when compared to baseline, but not when compared to the modafinil condition (M= 10.29, sd= 15.39, *p*= .034). For the other subschales, no other differences were found.

Table 13. Descriptive statistics of the SF-36 on baseline measure and the modafinil and placebo condition.

Measure	Baseline		Modafinil		Placebo	
	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Physical functioning	72.33(19.90)	30	77.29(20.89)	25	76.72 (24.03)	29
Role limitations due to physical health	17.50(28.73)	30	49.00(44.18)	25	47.12 (39.55)	29
Bodily pain	72.93(19.25)	30	74.70(23.27)	24	76.66 (17.41)	29
General health perceptions	51.60(20.38)	30	56.82(17.36)	24	57.00 (19.85)	29
Vitality	41.67(15.67)	30	51.94(18.08)	24	53.45 (15.01)	29
Social functioning	62.92(19.28)	30	69.20(19.98)	28	65.09 (20.15)	29
Role limitations due to emotional problems	63.33(40.45)	30	65.28(41.10)	24	66.67 (40.83)	29
Mental health	67.73(15.18)	30	65.42(17.34)	24	68.55 (18.60)	29
Physical component score (PCS)	40.47 (7.78)	30	45.91 (7.93)	24	44.87 (9.28)	29
Mental component score (MCS)	44.68 (9.97)	30	44.60(10.27)	24	45.50 (12.05)	29

Table 14. Analysis of the SF-36 comparing baseline measure and the modafinil and placebo condition.

Measure		*Z*	*P*
Physical functioning	Baseline -Modafinil	-2.28	.023*
	Baseline - Placebo	-2.04	.042*
	Modafinil - Placebo	-0.23	.815
Role limitations due to physical health	Baseline -Modafinil	-2.82	.005*
	Baseline - Placebo	-3.34	.001*
	Modafinil - Placebo	-0.57	.571
Bodily pain	Baseline -Modafinil	-0.52	.601
	Baseline - Placebo	-1.14	.255
	Modafinil - Placebo	-0.09	.931
General health perceptions	Baseline -Modafinil	-1.16	.247
	Baseline - Placebo	-1.71	.087
	Modafinil - Placebo	-0.38	.702
Vitality	Baseline -Modafinil	-2.47	.014*
	Baseline - Placebo	-3.12	.002*
	Modafinil - Placebo	-0.65	.519
Social functioning	Baseline -Modafinil	-1.58	.114
	Baseline - Placebo	-0.38	.706
	Modafinil - Placebo	-0.67	.500
Role limitations due to emotional problems	Baseline -Modafinil	-0.35	.729
	Baseline - Placebo	-0.35	.729
	Modafinil - Placebo	-0.24	.811
Mental health	Baseline -Modafinil	-1.01	.311
	Baseline - Placebo	-0.29	.776
	Modafinil - Placebo	-1.12	.263
Physical component score (PCS)	Baseline -Modafinil	-3.43	.001*
	Baseline - Placebo	-2.91	.004*
	Modafinil - Placebo	-0.34	.738
Mental component score (MCS)	Baseline -Modafinil	-0.11	.909
	Baseline - Placebo	-0.31	.754
	Modafinil - Placebo	-0.27	.784

* $p < .05$

Table 15. Descriptive statistics of the BN-20 on baseline measure and the modafinil and placebo condition.

	Baseline		Modafinil		Placebo	
Measure	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*	Mean (SD)	Sample size *N*
Future uncertainty	33.33 (21.99)	28	26.33 (21.06)	25	25.93 (23.15)	27
Visual disorder	18.01 (13.74)	29	12.89 (13.49)	25	12.70 (14.41)	28
Motor dysfunction	15.33 (22.30)	29	14.66 (13.87)	25	10.29 (15.39)	27
Communication deficit	22.61 (21.71)	29	18.37 (18.58)	26	19.83 (18.48)	28
Headaches	31.03 (28.07)	29	30.86 (34.50)	27	32.18 (27.43)	29
Seizures	8.04 (19.22)	29	13.33 (27.21)	25	6.90 (16.38)	29
Drowsiness	45.98 (31.39)	29	24.36 (27.58)	26	28.74 (31.78)	29
Bothered by hair loss	16.09 (26.16)	29	10.26 (22.64)	26	9.20 (19.73)	29
Bothered by itching of skin	19.54 (26.00)	29	11.11 (20.67)	27	13.79 (26.00)	29
Weakness of legs	10.34 (26.88)	29	8.64 (21.86)	27	4.60 (21.31)	29
Difficulties with bladder control	13.79 (24.43)	29	8.00 (17.43)	25	11.11 (24.46)	27

Table 16. Analysis of the BN20 comparing baseline measure and the modafinil and placebo condition.

Measure		*Z*	*P*
Future uncertainty	Baseline -Modafinil	-1.62	.105
	Baseline - Placebo	-1.79	.074
	Modafinil - Placebo	-0.02	.983
Visual disorder	Baseline -Modafinil	-2.39	.017*
	Baseline - Placebo	-3.08	.002*
	Modafinil - Placebo	-0.08	.936
Motor dysfunction	Baseline -Modafinil	-0.24	.808
	Baseline - Placebo	-2.12	.034*
	Modafinil - Placebo	-1.17	.244
Communication deficit	Baseline -Modafinil	-1.74	.082
	Baseline - Placebo	-1.32	.186
	Modafinil - Placebo	-1.06	.290
Headaches	Baseline -Modafinil	-0.08	.935
	Baseline - Placebo	-0.07	.942
	Modafinil - Placebo	-0.14	.885
Seizures	Baseline -Modafinil	-1.27	.206
	Baseline - Placebo	-0.72	.472
	Modafinil - Placebo	-1.55	.121
Drowsiness	Baseline -Modafinil	-3.78	<.001*
	Baseline - Placebo	-2.78	.005*
	Modafinil - Placebo	-0.85	.394
Bothered by hair loss	Baseline -Modafinil	-1.52	.129
	Baseline - Placebo	-1.46	.145
	Modafinil - Placebo	-0.45	.655
Bothered by itching skin	Baseline -Modafinil	-2.31	.021*
	Baseline - Placebo	-1.30	.194
	Modafinil - Placebo	-0.72	.472
Weakness of legs	Baseline -Modafinil	-1.16	.246
	Baseline - Placebo	-1.91	.056
	Modafinil - Placebo	-1.34	.180
Difficulties with bladder control	Baseline -Modafinil	-1.13	.257
	Baseline - Placebo	-0.58	.564
	Modafinil - Placebo	-0.45	.655

* $p < .05$

Discussion

In the current study, the effect of modafinil on fatigue, cognitive functioning, depression and overall quality of life was examined in patients with a primary brain tumor. It was hypothesized that modafinil would have a positive effect on all outcome measures. The study was built on a earlier study of Gehring et al. (2012), taking limitations into account by using a double-blind placebo controlled crossover design.

Regarding fatigue, earlier studies showed that modafinil reduced the symptoms of fatigue in various patient populations (Brown, Howard & Kemp, 2010; Blackhall et al., 2009). It was expected that modafinil would have a positive effect on fatigue in patients with a primary brain tumor.
For overall fatigue, an effect of both modafinil and placebo was found, indicating that patients are less fatigued in both conditions compared to baseline. Since we found no difference in effect between the two conditions, this may be attributable to a placebo-effect. The most common definition of this effect is provided by Wolf: "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties"(Wolf, 1959).
Addionally, we found a separate negative effect in the modafinil condition on the subscale 'Fatigue severity'. This indicates that the use of modafinil, but not that of a placebo, increased the severity of fatigue. On the subscale 'Reduced motivation', we found a separate negative effect of placebo. This implies that patients have a lower degree of reduced initiative and motivation when they use a placebo. For fatigue, the present results do not match the findings of earlier studies and also do not correspond with the formulated expectations.

With respect to cognition, earlier studies found evidence of a positive effect in patients with psychiatric conditions (ADHD, depression and syndromes of fatigue) and in breast cancer survivors (Rugino & Copley, 2001; Minzenberg & Carter, 2008; Kohli et al., 2009). Modafinil in particular seemed to have an effect on attention and the storing, retaining, and retrieving both verbal and visual information (Kohli et al., 2009). It therefore was hypothesized that modafinil would improve cognitive functioning in patients with a primary brain tumor, particularly in the domains attentional functioning and working- and verbal memory. In the present study a trend was found indicating a positive effect of modafinil on working memory. This implies that working memory improves when modafinil is used, but not when a placebo is used. A placebo-effect was found in the cognitive domains attentional functioning and psychomotor control.

When a distinction was made between patients who were impaired in three or more cognitive domains at baseline and those who were not, different effects were found. In this group, a placebo effect was found for the domains executive functioning, working memory and information processing speed. In the domains information processing and verbal memory, the use of modafinil and placebo both had an effect, although the use of a placebo had a larger effect than modafinil. This indicates that information processing and verbal memory improve when patients who have cognitive impairments use modafinil, but that it improves even more when they use a placebo. In contrast to results of the whole participant group, modafinil has no separate effects on working memory. This matches neither the results of earlier studies nor the expectations of the present study.

Aside from performance on neuropsychological tests, subjective self-reported cognitive functioning was examined. It was expected that the use of modafinil would also relieve the cognitive complaints of patients with a primairy brain tumor. The use of modafinil had a negative effect on reported sustained attention, an effect that was not found when placebo was used. This indicates that the use of modafinil lowers perceived sustained attention. We also found that when either modafinil or placebo was used, patients experience more difficulties in day-to-day functioning with problem solving and concentrating. In conclusion, the results showed the opposite of what was expected.

With respect to depression, according to results from earlier studies, modafinil seemed effective in treating cancer patients with depressive symptoms (Blackhall et al., 2009). It was therefore expected that modafinil would also reduce symptoms of depression in patients with a primary brain tumor. However, no separate effect of modafinil was found; which resulted in the rejection of our earlier assumptions.

Concerning overall quality of life, beneficial effects of modafinil were found for patients with Multiple Sclerosis and cancer (Brown, Howard & Kemp, 2010; Blackhall et al., 2009). It was hypothesized that the drug would also increase the overall QOL in patients with a primary brain tumor. However, this hypothesis had to be rejected since no separate effect of modafinil was found.

In addition to the hypothesized outcomes, the effect of modafinil on neurological functioning was also examined. Just like for depression and QOL, we found no separate effect of modafinil on

neurological functioning.

In summary, less effects of modafinil were found than we expected beforehand. In the present study, modafinil seems to slightly improve working memory. On the other hand, the drug seems to increase the severity of fatigue in patients with a primary brain tumor, meaning it reduces the behavioural consequences of fatigue they experience in day-to-day life (Vercoulen et al., 1999). Additionally, modafinil seems to decrease patient-reported sustained attention.

These findings are in contrast with earlier results from the study of Gehring et al. (2012). They found significant effects of modafinil in the cognitive domain 'Information processing speed' as well as a general beneficial effect on measures of fatigue, depression and QOL (Gehring et al., 2012). However, these results were interpreted with caution, due to the absence of a placebo control group and a cross-over design and the the fact that they used a small sample size. The difference in results between this study and the present one may be explained by our use of a cross-over design and a placebo condition.

Remarkebly, the results of the present study also do not correspond with earlier findings in patient populations with other types of cancer or other psychiatric symptoms. In patients with a primary brain tumor, the cognitive deficits are more often more severe than in patients with other types of cancer. Additionally, the symptoms of depression may be caused by the neurological consequences as a result of their disease, but may also be a reaction to physical and cognitive limitations they experience and to the prognosis they received. This differs greatly from the causes of depression in patients with psychiatric ilnessess. Consequently, these complex combination of factors in which patients with a primary brain tumor differ from other patient groups, may be explain why we found a different efficacy of modafinil in the present study.

Strikingly, on most of the outcome measures in the present study, the use of placebo has the same effect as modafinil itself. As earlier suggested, when modafinil and placebo show the same efficacy, there is a placebo effect. Although double-blind randomized placebo-controlled crossover trials, like the present study, were designed to account for such an effect, there are still several explanations for its occurrence. For example, the masking component of the double-blind randomized controlled trial (RCT) might contribute to a bias (Kaptchuk, 2001). When patients know that there is a chance they could receive a placebo, this uncertainty is enough to decrease the magnitude of the effect of either the drug or placebo. On the other hand, the opposite effect can

occur as well. Participation in an RCT may increase the sensitivity and vigilance of the subject (and the clinician). This 'expectation of benefit' may increase the detection of beneficial responses (de la Fuente-Fernández, Schulzer & Stoessl, 2002). This means that aside from the occurrence of a possible effect related to the treatment itself (the pharmacological properties of the drug), there also is an effect inherent in the perception that treatment is being received. Specific neural circuits and neurotransmitter systems respond to the expectation of benefit during placebo administration, inducing measurable physiological changes (Zubieta & Stohler, 2009). In the current study both of these effects might have influenced the study outcome.
Aside from the placebo effect there is a possibility that factors such as the effect of medical care and the relationship between patient and physician have contributed to the perception of clinical benefit in both the modafinil and placebo conditions (de la Fuente-Fernández et al., 2002).

For some results, such as reduced motivation regarding fatigue and for the performance on the cognitive domains attentional functioning and psychomotor control, the placebo seemed more efficacious than modafinil. This may be explained by the possible experience of side effects in the modafinil condition that affected their attention and psychomotor control and influenced their self-reports of motivation. An explanation for the notable findings in the placebo condition may be 'the expectation of benefit' in combination with the absence of negative effects drug side-effects can have on patients' wellbeing.

Despite improvements in the study design compared to previous publications, the present study has its limitations. Due to the relatively small sample size, the results should be interpreted with caution. During the sample size calculations and recruitment of participants for this study, it was taken into account whether patients had cognitive deficits and symptoms of fatigue and depression, but not whether they were sufficiently motivated to participate to the study. Patients often found it too burdensome to receive treatment for (neuro-) psychological symptoms after the intensive medical treatment they already received for the brain tumor (resection and/or chemo- and radiation therapy). Disadvantages of participating in the study, such as additional hospital visits and drug side-effects, outweighed the potential benefits for a large part of the eligible participants. These difficulties led to a slow accrual. As a result, only a relatively small sample was formed when the end of the financial budget was reached.

Another important remark must be made concerning the diversity in tumor type within the participant group. Patients with meningiomas as well as low-grade and high-grade gliomas

participated in the study (see Table 1). Most types of gliomas are rarely curable and will eventually be fatal to the patient. Meningeomas, on the other hand, are benign and can often be considered a chronic illness. These patients have to live with the impairments as consequences of the tumor and its treatment and have to incorporate these impairments in their vision of the future. The difference in prognosis affects the type and degree of the psychological symptoms patients experience. This in turn may influence the efficacy of modafinil. Future research should take these differences in account.

Despite these limitations, the current study is a good addition to previous studies on the efficacy of modafinil on (neuro-)psychological symptoms and overall QOL in primary brain tumor patients. The benefit of this present study is its design; a double-blind placebo controlled crossover trial. Even though there may still be a placebo-effect when this design is used (as was mentioned earlier) it is a standardized, explicit, replicable and impersonal procedure that defines unambiguous and formal norms for researchers (Kaptchuk, 2001). The double-blind RCT is the least subjective and most impersonal procedure ethically possible now.

As previous studies suggested that modafinil may be more efficacious in participants with greater impairment at baseline measure (Gehring et al., 2011b), the present study took this into account. The effects found for patients who were cognitively impaired at baseline differed from those who were not impaired. Even though we did not find a separate effect of modafinil, an effect might be found when the present limitations are taken in consideration.

The current study provides evidence for a beneficial effect of modafinil on working memory, but also for a negative effect on fatigue severity and patient-reported sustained attention. More work is needed to be more definitive about the found effects and future research may build on the discussed strengths and weaknesses of the current study. Since the results of the present study show no major effects of modafinil in patients with a primary brain tumor, other options pharmaceutical treatment, such as methylphenidate, should also be further explored for this patient group. Since many patients found it too burdensome to use drugs to alleviate their symptoms, other interventions such as cognitive behavioral therapy or cognitive rehabilitation may be more suitable options and should therefore be explored in future research. The alleviation of (neuro-) psychological symptoms and overall QOL could significantly improve the wellbeing of patients with a primary brain tumor.

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