The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial

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Background. Fatigue, cognitive deficits, and depression are frequently reported but often undertreated symptoms that can profoundly affect daily life in patients with primary brain tumors (PBTs). To evaluate the effects of the psychostimulant modafinil on fatigue, depression, health-related quality of life (HRQOL), and cognitive functioning in PBT patients, we performed a multicenter, double-blind placebo-controlled crossover trial.
Methods. Patients randomly received either 6 weeks of treatment with modafinil (up to 400 mg/day) or 6 weeks with placebo. After a 1-week washout period, the opposite treatment was provided. Assessments took place at baseline and immediately after the first and second condition. Patients completed self-report questionnaires on fatigue (Checklist Individual Strength [CIS]), depression (Center for Epidemiologic Studies Depression Scale [CES-D]), HRQOL (Short-Form Health Survey [SF-36]), and self-perceived cognitive functioning (Medical Outcomes Study [MOS]). They also underwent comprehensive neurocognitive testing.
Results. In total, 37 patients participated. Relative to baseline, patients reported lower fatigue severity (CIS) and better motivation (CIS) in both the modafinil ($P = .010$ and $P = .021$, respectively) and the placebo condition ($P < .001$ and $P = .027$, respectively). The same held for physical health (SF-36 Physical Component Summary score; $P = .001$ and $P = .008$, respectively), working memory ($P = .040$ and $P = .043$), and information processing capacity ($P = .036$ and $P = .040$). No improvement in depressive symptoms was found in either condition.
Conclusions. Modafinil did not exceed the effects of placebo with respect to symptom management. Patient accrual was slow, and relatively many patients dropped out during the trial, due mostly to side effects. Other, preferably nonpharmacologic intervention studies should be considered to improve symptom management of PBT patients.

Keywords: brain tumor, cognitive functioning, fatigue, HRQOL, modafinil, mood.

Fatigue, cognitive deficits, and depression are frequently reported symptoms in patients with primary brain tumors (PBTs).[1,2] Over 80% of PBT patients treated with cranial irradiation experience some degree of somnolence, defined as symptoms of drowsiness, lethargy, and fatigue.[3,4] Unrelated to radiation treatment, 39% of long-term survivors of low-grade glioma report severe symptoms of fatigue.[5] In addition to fatigue, cognitive impairments are experienced by 80% of PBT patients.[6] The prevalence of depression in PBT patients ranges from 15% to 27%.[7] All of these symptoms have a large impact on the everyday life of patients and may lead to a significant decrease in health-related quality of life (HRQOL).[8] It is suggested that effective treatment of these symptoms may increase HRQOL,[9] although an optimal strategy to reach this goal has not been defined yet.

Modafinil (2-benzhydrylsulfinylethanamide) is a wakefulness-promoting agent that targets fatigue, cognitive functioning, and mood. Although categorized as a psychostimulant, it differs from amphetamine in both physiological and behavioral aspects. It is highly selective for the central nervous system, has a lower abuse

potential, and poses a lower risk for adverse effects on organ systems.[10–14] The precise mechanism of action of modafinil is unknown, but it is theorized to act in a localized manner, utilizing hypocretin, histamine, epinephrine, γ-aminobutyric acid (GABA), and glutamate.[10] It enhances catecholaminergic signaling and decreases GABA release, primarily at the level of the anterior hypothalamus and locus coeruleus.[11,15] It has been shown to bind directly to dopamine and norepinephrine receptors.[14] Forty percent to 65% of modafinil is readily absorbed, with only 10% of the drug being excreted in the urine in unchanged form.[14,16] Modafinil appears to target the sleep-wake centers of the brain more specifically than other psychostimulants.[11,12] With a half-life of 12–15 h,[14,16] modafinil requires only a single daily dose for efficacy. Lower dosages (50–200 mg/day) are generally prescribed for fatigue and concentration problems, while higher dosages (up to 600 mg/day) are used for daytime sleepiness in narcolepsy.[17] Although originally marketed for the latter,[18,19] modafinil has recently been found to be of use in improving fatigue,[20–27] mood,[28–31] and overall HRQOL[32] in several study populations. Moreover, there is evidence that it may even enhance cognitive functioning.[14,33–36] In healthy adults, working memory, recognition memory, sustained attention, and cognitive control are improved after modafinil.[14,36] In children and adolescents with attention deficit hyperactivity disorder (ADHD), improved attention and response inhibition have been reported, while in several adult psychiatric populations, modafinil appears to improve cognitive functions that depend on prefrontal structures.[14] In patients with schizophrenia, especially working memory and problem-solving abilities improved.[34]

Despite these potentially beneficial effects, notably little is known about the effects of modafinil on symptom management in PBT patients. Compared with modafinil, methylphenidate is more similar to amphetamine in its pharmacologic profile. It inhibits dopamine and norepinephrine uptake and increases concentrations of these neurotransmitters in the brain.[37] It targets primarily the prefrontal cortex.[38] Immediate-release methylphenidate has a relatively short half-life, which necessitates 2 or 3 doses a day, while sustained-release methylphenidate requires only a single dose per day.[39] In an open-label pilot study, 24 PBT patients were randomly assigned to 4 weeks of modafinil (200 mg q.d.), immediate-release methylphenidate (20 mg b.i.d.), or sustained-release methylphenidate (18 mg q.d.).[39] Comparison of combined immediate- and sustained-release methylphenidate with modafinil showed the latter to have significant positive effects on information-processing speed and executive functioning requiring divided attention. Additionally, a general beneficial effect of both methylphenidate and modafinil on fatigue, mood, and HRQOL was found.[39] Another pilot study, presented at the 2006 annual meeting of the American Society of Clinical Oncology, that had a double-blind dose-controlled randomization of 200 or 400 mg/day of modafinil for 3 weeks, a washout period of 1 week, and an open label extension of 8 weeks, also reported decreased fatigue and improvements in cognitive functioning and mood in

PBT patients, although final results have not been published yet.[40] Presently, we performed a multicenter, double-blind placebo-controlled crossover trial to evaluate the effects of modafinil on fatigue in PBT patients. As fatigue may interact with functional activities and HRQOL, and considering the encouraging study results described above, the effects of modafinil on cognition, mood, and overall HRQOL were also evaluated.

Materials and Methods

Participants

We identified patients who visited the outpatient departments of 3 tertiary referral centers for neuro-oncology (VU University Medical Center, Amsterdam; Academic Medical Center, Amsterdam; and Medical Center Haaglanden, the Hague) between January 2009 and December 2011. Participants were eligible if they (i) were ≥ 18 years old, (ii) had been diagnosed with a histologically confirmed glioma or meningioma (collectively called PBT throughout this report), and (iii) had no signs of tumor recurrence in the last 6 months. In addition, they were invited to participate only if they reported a heightened experience of fatigue (score >27 on the Checklist Individual Strength [CIS][41]), as this was our primary outcome measure. Patients were excluded if (i) they had a history of psychiatric disease or symptoms, including depressive disorders; (ii) adverse interactions between modafinil and other prescribed medications were expected (eg, decreased effectiveness of oral contraceptives, levonorgestrel-releasing intrauterine systems and antidepressants, fluctuations in the effectiveness of antiepileptic drugs acting on similar enzymes); (iii) they were unable to communicate in Dutch. A priori sample size calculations based on statistical power (1-β) of 0.80, $r = 0.30$ and $\alpha = 0.05$, yielded 64 patients to be included in the study. The study was approved by the institutional review boards of all participating centers and was registered at http://www.clinicaltrialsregister.eu/ with EudraCT number 2007-003102-10. All patients provided written informed consent.

Procedure

Eligible patients were introduced to the trial by their treating physician either in person or by mail. The researchers then contacted the patients by telephone to inquire if they were interested in participating. As fatigue was our primary outcome measure, interested patients were asked to fill out the CIS to assess the severity of their complaints and their suitability for participation. After obtaining informed consent, sociodemographic and clinical data were collected from patients' medical records. A pharmacy randomization system was used to assign participants to either the modafinil or the placebo condition, while patients, treating physicians, and researchers were blind to treatment allocation. Patients received 6 weeks of treatment with either modafinil or placebo starting with a 100-mg dose upon waking and at lunch

(200 mg/day in total). After the first week, the dose was doubled to 400 mg/day. After treatment period 1, a washout period of 1 week was applied. Hereafter, the opposite treatment was provided during treatment period 2 (ie, those who first received modafinil now received placebo and vice versa). During the trial, patients were asked not to take benzodiazepines, as these might interfere with modafinil. Assessments took place at baseline (T1), immediately after treatment period 1 (after 6 wk; T2), and immediately after treatment period 2 (after 12 wk; T3). These assessments included self-report questionnaires and neuropsychological assessment, as well as physical and neurological examination carried out by a physician. If patients experienced adverse effects, they were allowed to decrease the medication to the lower dose (200 mg/day) or to stop participating in the trial after consulting the physician involved in the trial.

Patient-Reported Outcomes

Patients were asked to complete self-report questionnaires on measures of fatigue as the primary outcome measure and depression, HRQOL, and subjective cognitive functioning as secondary outcome measures.

Checklist Individual Strength (CIS).[41]—Fatigue was assessed with this multidimensional scale; each item was scored on a 7-point Likert scale. The CIS includes 4 aspects of fatigue (fatigue severity, concentration problems, reduced motivation, and reduced activity) and a total score. High scores indicate a high level of fatigue, a high level of concentration problems, low motivation, and a low activity level. Based on normative controls, a total score between 27 and 35 indicates a heightened experience of fatigue.

Center for Epidemiologic Studies Depression Scale (CES-D).[42]—This 20-item questionnaire was used to assess symptoms of depression. Participants were asked to indicate on a 4-point scale how often they felt that a statement was applicable to their situation during the past week. Scores range between 0 and 60, with higher scores indicating more feelings of depression. In the general population, respondents with a total score of ≥16 are considered depressed.

Medical Outcomes Study Short-Form Health Survey (SF-36).[43]—This HRQOL survey is composed of 36 items that are organized into 8 multi-item scales assessing (i) physical functioning, (ii) limitations in role functioning due to physical problems, (iii) limitations in role functioning due to emotional problems, (iv) pain, (v) vitality, (vi) social functioning, (vii) mental health, and (viii) general health perceptions. From these scales, 2 higher-order summary scores can be calculated: (i) the Physical Component Summary (PCS), measuring physical health and (ii) the Mental Component Summary (MCS), measuring mental health. In a normative sample from the general population, PCS and MCS scores have a mean of 50 with a standard deviation of 10.

MOS subjective cognitive functioning scale.[44]—This 6-item scale assesses everyday problems in cognitive functioning, including difficulty with reasoning and problem solving, slowed reaction time, and problems with concentration (range, 1–6).

Objective Cognitive Functioning

Using an extensive battery of neuropsychological tests, objective cognitive functioning was assessed. Tests included measures of verbal memory (Auditory Verbal Learning Test[45]), working memory (Memory Comparison Test[46]), attentional functioning (Stroop Color Word Test[47]), information processing (Letter Digit Substitution Test[48]), executive functioning (Concept Shifting Test,[49] Categorical Word Fluency Test[50]), and psychomotor speed (Concept Shifting Test, Letter Digit Substitution Test).

Statistical Analysis

All statistical analyses were performed with SPSS software version 20. Standard scoring rules were applied to convert the data from the questionnaires. Mean imputation was used to handle missing values within completed questionnaires or neuropsychological assessments. To assess a change in cognitive functioning as accurately as possible, cognitive test scores were converted to z-scores using the means and SDs of the patients' scores at baseline. To achieve data reduction, 6 cognitive domains were formed (verbal memory, working memory, attentional functioning, information processing, executive functioning, and psychomotor speed; Table 3). Construction of these cognitive domains was based on a principal component analysis using Varimax rotation with Kaiser normalization performed on the z-scores of an extensive study among healthy subjects into the biological predictors of cognitive aging.[51] 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, depression, the PCS and MCS scales of the SF-36 (HRQOL), and subjective and objective cognitive functioning. Given the small sample size, no corrections for multiple statistical testing were applied. A P-value of ≤.05 was considered statistically significant; $P \leq .10$ was considered a trend.

Results

Patient Characteristics

Figure 1 shows details of the participant flow. In total, 155 PBT patients were assessed for eligibility. A total of 39 (25.2%) patients met the inclusion criteria, agreed to participate, and subsequently signed the informed consent form. Thirty-seven patients were assigned randomly to a treatment condition, whereas 2 patients dropped out before randomization because they were no longer
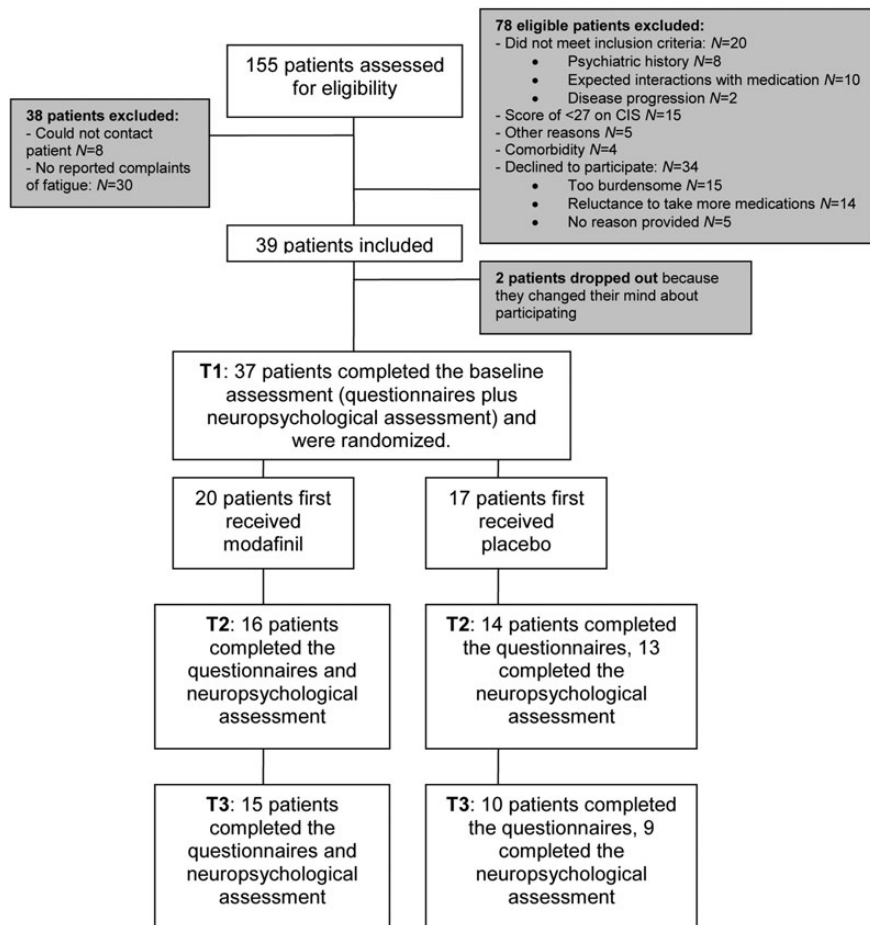
Fig. 1. Participant flow.

willing to participate. During the trial, overall 12 patients dropped out: 7 dropped out between T1 and T2, and 5 dropped out between T2 and T3. Reasons for not completing the trial were discontinuation of medication due to side effects ($n = 7$; patients reported a tingling sensation, nausea, vertigo, anxiety, depression, and feeling fidgety), missed follow-up ($n = 4$), and disease progression ($n = 1$). Table 1 presents sociodemographic and clinical characteristics of the study sample. The mean age of participants was 42.2 years, and more women than men participated (62.2% vs 37.8%). Most participants had a low-grade glioma (37.8%), and the mean time since diagnosis was 49.5 months.

Patient-Reported Outcomes

Fatigue—As can be seen in Table 2, scores on the CIS scales for fatigue severity and reduced motivation were significantly lower after treatment with both modafinil ($P = .010$ and $P = .021$, respectively) and placebo ($P < .001$ and $P = .027$, respectively) compared with the baseline assessment. The extent of decrease in fatigue as measured by these scales, however, did not significantly differ between the 2 conditions. Although not statistically significant, a trend can be seen for an

improvement in reduced activity in the placebo condition ($P = .093$) compared with baseline. On the total CIS score, patients' symptoms were alleviated in both the modafinil and placebo conditions ($P = .005$ and $P = .001$, respectively), while scores between the experimental conditions did not differ.

Depression—Scores on the CES-D did not differ significantly between treatment conditions. At baseline, reported scores were only slightly higher ($M = 15.86$, $SD = 9.49$) than in both the modafinil and placebo conditions ($M = 14.16$, $SD = 9.06$ and $M = 13.97$, $SD = 9.44$, respectively; $P =$ n.s.). All mean scores were within the nondepressed range (ie, <16).

Health-related quality of life—Patients' physical health as measured by the PCS scale improved significantly after treatment with both modafinil ($M = 46.05$, $SD = 7.96$) and placebo ($M = 44.71$, $SD = 9.13$) compared with baseline ($M = 40.60$, $SD = 7.58$; $P = .001$ and $P = .008$, respectively). No other significant differences were observed for either physical or mental health scales.

Subjective cognitive complaints—A trend was observed where participants tended to report higher self-perceived

Table 1. Demographic and clinical characteristics of the study sample

	Participants (n = 37)
Age, y M (SD)	48.16 (12.02)
Gender n (%)	
Male	14 (37.8%)
Female	23 (62.2%)
Educational level n (%)	
Low	10 (27.0%)
Medium	15 (40.5%)
High	11 (29.7%)
Other	1 (2.7%)
Marital status n (%)	
Single	7 (18.9%)
Married or living together	25 (67.6%)
Divorced	2 (5.4%)
Widow(er)	3 (8.1%)
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 n (%)	
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 lateralization 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 mo n (%)	18 (48.6%)
>36 mo n (%)	19 (51.4%)
Medication use prior to trial n (%)	
Antiepileptic drugs	20 (54.1%)
Antihypertensive drugs	8 (21.6%)
Cholesterol inhibitors	4 (10.8%)
Anticoagulants	3 (8.1%)
Analgesics (mild opioids)	2 (5.4%)
Analgesics (non-opioids)	1 (2.7%)

Continued

Table 1. *Continued*

	Participants (n = 37)
Antiallergic drugs	2 (5.4%)
Bladder control drugs	2 (5.4%)
Stomach protectors	2 (5.4%)
Laxatives	2 (5.4%)
Benzodiazepines	2 (5.4%)
Anorexiants	1 (2.7%)
Progestagens	1 (2.7%)
Oral contraceptives	1 (2.7%)
Change in medication use during trial n (%)	
Analgesics (non-opioids)	4 (10.8%)
Antibiotics	3 (8.1%)
Flu vaccine	1 (2.7%)
Antidiabetics	1 (2.7%)
Antiemetics	1 (2.7%)
Radiotherapy (ever) n (%)	
Yes	16 (43.2%)*
No	21 (56.8%)
Chemotherapy (ever) n (%)	
Yes	8 (21.6%)*
No	29 (78.4%)
Progressive disease during intervention n (%)	
Yes	2 (5.4%)
No	35 (94.6%)

*One participant had received radiotherapy not involving the CNS and chemotherapy for breast cancer, not for PBT. The patient did not have brain metastases.

cognitive functioning after treatment with placebo compared with baseline (P = .056; Table 3).

Objective Cognitive Functioning

Table 3 shows that patients improved after treatment with both modafinil and placebo compared with baseline for both the working memory domain (P = .040 and P = .043, respectively) and the information-processing domain (P = .036 and P = .040, respectively). Scores did not differ between the experimental conditions. For attentional functioning, scores improved significantly after the placebo treatment compared with baseline (P = .015) and after modafinil treatment (P = .013).

Discussion

Contrary to our hypotheses, we did not find beneficial effects of modafinil on fatigue, depression, overall HRQOL, or cognitive functioning in comparison with placebo. Patients reported a decrease in fatigue severity, an improvement in reduced motivation, and a better overall fatigue score in both the modafinil and the placebo condition compared with baseline, indicating a placebo effect. Counterintuitively, a trend was found for an improvement in the reduced activity scale after the placebo condition, but not after the modafinil

Table 2. Results of comparisons between the baseline assessment and the modafinil and placebo conditions for fatigue (CIS)

Bas n = 36 M (SD)	Mod n = 26 M (SD)	Pla n = 29 M (SD)	Bas vs Mod z (P)	Bas vs Pla z (P)	Mod vs Pla z (P)
Concentration problems					
20.75 (9.18)	18.85 (7.90)	19.91 (8.36)	−1.10 (.270)	−1.15 (.252)	−0.97 (.331)
Reduced motivation					
17.00 (5.40)	14.38 (5.72)	14.86 (6.72)	−2.31 (.021*)	−2.22 (.027*)	−3.38 (.702)
Reduced activity					
13.49 (4.87)	11.58 (5.34)	12.59 (5.17)	−1.37 (.170)	−1.68 (.093)	−0.43 (.671)
Fatigue severity					
41.72 (9.22)	34.92 (12.04)	35.14 (10.86)	−2.56 (.010*)	−3.72 (<.001*)	−0.75 (.456)
Total score					
93.80 (20.16)	79.73 (26.45)	82.48 (26.26)	−2.83 (.005*)	−3.35 (.001*)	−1.01 (.313)

Abbreviations: Bas, baseline; Mod, modafinil; Pla, placebo.
*P < .05.

Table 3. Overview of cognitive tests administered and results of comparisons between the baseline assessment and the modafinil and placebo conditions for cognitive functioning

Baseline n = 36 M (SD)	Modafinil n = 25 M (SD)	Placebo n = 28 M (SD)	Baseline vs Modafinil z (P)	Baseline vs Placebo z (P)	Modafinil vs Placebo z (P)
Verbal memory					
Auditory Verbal Learning Test (AVLT)[45]					
0.00 (0.71)	0.14 (0.86)	−0.12 (1.02)	−1.63 (.104)	−0.29 (.767)	−1.60 (.110)
Working memory					
Memory Comparison Test (MCT)[46]					
0.00 (0.86)	0.24 (0.93)	0.17 (0.90)	−2.06 (.040*)	−2.03 (.043*)	−1.26 (.209)
Attentional functioning					
Stroop Color Word Test[47]					
0.00 (1.04)	0.15 (0.94)	0.18 (0.75)	−1.28 (.201)	−2.44 (.015*)	−2.49 (.013*)
Information processing					
Letter Digit Substitution Test (LDST)[48]					
0.00 (0.94)	0.36 (1.18)	0.19 (1.12)	−2.01 (.036*)	−2.05 (.040*)	−0.24 (.808)
Executive functioning					
Concept Shifting Test (CST)[49]					
Categorical Word Fluency Test (CWFT)[50]					
0.00 (0.80)	0.19 (0.78)	0.05 (0.94)	−1.17 (.242)	−1.25 (.210)	−0.03 (.977)
Psychomotor speed					
Concept Shifting Test[40]					
Letter Digit Substitution Test[48]					
0.02 (0.61)	0.26 (0.56)	0.16 (0.53)	−1.60 (1.09)	−1.48 (.139)	−0.54 (.587)
Subjective cognitive functioning					
31.79 (17.62)	29.11 (16.04)	27.49 (18.11)	−0.79 (.428)	−1.91 (.056)	−1.33 (.184)

The cognitive domains included the following assessments: verbal memory: AVLT 1, AVLT recall, AVLT recognition, AVLT delta, AVLT total; working memory: MCT %, MCT 1, MCT 2, MCT 3, MCT4; attentional functioning: Stroop card 1, Stroop card 2, Stroop card 3; information processing: LDST reading, LDST writing; executive functioning: CST A, CST B, CST C, CWFT animals (60 s); psychomotor speed: CST 0, LDST delta.
*P < .05.

condition. For depression, overall HRQOL, and cognitive functioning, we found no difference between the treatment conditions.

In different study samples of patients with various neurological conditions (Charcot-Marie-Tooth disease, fibromyalgia, amyotrophic lateral sclerosis, multiple sclerosis, schizophrenia, narcolepsy), beneficial effects of modafinil for symptoms of fatigue, HRQOL, and cognitive functioning have been shown.[21–24,26,27,32,35] However, the majority of these studies were not placebo controlled, and study samples were often relatively small. Although the literature on modafinil for symptom management in PBT patients is scarce, 2 studies have been reported and both showed positive results. Gehring

et al.[39] reported beneficial effects of both modafinil and methylphenidate for patient-reported measures of fatigue, mood, and HRQOL as well as for objective neuropsychological testing. However, no differences between treatment arms over time were reported for fatigue, mood, and HRQOL, and findings with regard to cognitive functioning were inconsistent, indicating that nonspecific treatment effects may have played a role. In an unpublished pilot study, Kaleita et al.[40] mention improvement in fatigue, mood, and cognitive functioning in PBT patients randomized to either a 200-mg or a 400-mg modafinil dose. However, since the results of Kaleita et al. remain unpublished, we cannot properly compare their methodology to ours. Importantly, in both studies, no placebo condition was used. As psychological mechanisms such as the presence of expectations prove to be powerful aspects of the experienced effects of medication use,[52] it seems likely that the beneficial effects reported in these previous studies could at least, in part, be attributable to a placebo effect.

Despite this methodological advantage of the present study, there are also significant limitations. In spite of great efforts in recruiting patients, accrual was difficult, and ultimately, we did not reach the required sample size. As shown in Fig. 1, almost half of the eligible patients declined participation for several reasons, such as expecting participation to be too burdensome or declining to take more drugs than was strictly necessary. Furthermore, during the trial, a considerable number of patients (32%) dropped out for various reasons, although the majority of these (58.3%) decided to discontinue medication because of side effects. Interestingly, this also included patients in the placebo condition who should not have experienced any side effects. Although it is not uncommon to experience side effects with placebo use,[53] the fact that these patients dropped out of the trial does suggest that possibly pharmaceutical trials for symptom management are less suitable for PBT patients. Another study limitation is the heterogeneity of the patient population. We included patients with meningiomas as well as gliomas, while these diseases are not equal in many respects (eg, nature of the disease, symptoms and treatment, prognosis). Although there is no indication that modafinil would be more effective in one subgroup of PBT patients than in another, it would have been preferable to study the effects of modafinil in a larger, more homogeneous group of patients.

Despite these limitations, we did find clear differences between the baseline assessment and outcome after both treatment conditions. This suggests that our lack of evidence for beneficial effects of modafinil for symptom management of PBT patients cannot be attributed to the small sample size. Rather, the participants in our sample did not experience better results from modafinil than from placebo. Given the apparent reluctance of a relatively large proportion of PBT patients to participate in pharmacologic trials for symptom management, as is shown in the present study as well as in the study by Gehring et al.,[39] and given the high percentage of patients suffering from fatigue, cognitive deficits, and mood disorders, other intervention studies should be considered. Concerning fatigue, Armstrong and Gilbert[54] provided an interesting overview of the guidelines of the National Comprehensive Cancer Network in relation to PBT patients. Although many nonpharmacologic interventions to treat fatigue (eg, activity enhancement, physically based therapy, psychosocial interventions, nutritional consultation, cognitive behavioral therapy for sleep hygiene) have been proven to be effective in the general cancer patient population, randomized controlled trials in PBT patients have not yet been performed. Concerning cognitive deficits, a cognitive function training program has been proven to be effective in PBT patients.[55] For depressive symptoms, nonpharmacologic intervention studies in this patient population are also still scarce, although many therapeutic interventions already exist for different cancer patient populations.[56] Because of their unique symptom pattern with neurological and cognitive sequelae, PBT patients are not easily comparable to other cancer patient groups. Therefore, the efficacy of the majority of interventions remains to be evaluated in this particular patient population. We recommend the development of nonpharmacologic interventions aimed specifically at symptom management in PBT patients, which may alleviate their symptom burden substantially and could improve their HRQOL significantly.

Acknowledgments

Conflict of interest statement. None declared.

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