Chapter 2.3

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

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The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multi-center, randomized placebo-controlled trial.  
ABSTRACT

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 six weeks of treatment with modafinil (up to 400mg/day) or six weeks with placebo. After a one week washout period, the opposite treatment was provided. Assessments took place at baseline and immediately after the first and second condition. Patients completed self-reported questionnaires on fatigue (CIS), depression (CES-D), HRQOL (SF-36), and self-perceived cognitive functioning (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) both in the modafinil ($p=0.010$ and $p=0.021$, respectively) and placebo condition ($p=0.001$ and $p=0.027$, respectively). The same held for physical health (SF-36 PCS score; $p=0.001$ and $p=0.008$, respectively), working memory ($p=0.040$ and $p=0.043$, respectively) and information processing capacity ($p=0.036$ and $p=0.040$, respectively). 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 nonpharmacological intervention studies should be considered to improve symptom management of PBT patients.
INTRODUCTION

Fatigue, cognitive deficits, and depression are frequently reported symptoms in patients with primary brain tumors (PBTs). Over 80% of PBT patients treated with cranial irradiation experience some degree of somnolence, defined as symptoms of drowsiness, lethargy and fatigue. Unrelated to radiation treatment, 39% of long-term survivors of low-grade glioma (LGG) report severe symptoms of fatigue. In addition to fatigue, cognitive impairments are experienced by 80% of PBT patients. The prevalence of depression in PBT patients ranges from 15% to 27%. 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). It is suggested that effective treatment of these symptoms may increase HRQOL, 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 of adverse effects on organ systems. 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. It enhances catecholaminergic signaling and decreases GABA release, primarily at level of the anterior hypothalamus and locus coeruleus. It has been shown to bind directly to dopamine and norepinephrine receptors. Forty to sixty-five percent of modafinil is readily absorbed, with only 10% of the drug being excreted in the urine in unchanged form. Modafinil appears to target the sleep-wake centers of the brain more specifically than other psychostimulants. With a half-life of 12 to 15 hours, 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. Although originally marketed for the latter, modafinil has recently been found to be of use in improving fatigue, mood and overall HRQOL in several study populations. Moreover, there is evidence that it may even enhance cognitive functioning. In healthy adults, working memory, recognition memory, sustained attention and cognitive control are improved after modafinil. 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. In patients with schizophrenia, especially working memory and problem-solving abilities improved.

Despite these potentially beneficial effects, notably little is known about the effects of modafinil on symptom management in PBT patients. Compared to 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. It targets primarily the prefrontal cortex. Immediate-release methylphenidate has a relatively short half-life, which necessitates two or three doses a day, while sustained-release methylphenidate only requires a
In an open label pilot study, 24 PBT patients were randomly assigned to four weeks of modafinil (200 mg q.d.), immediate-release methylphenidate (20 mg b.i.d.), or sustained-release methylphenidate (18 mg q.d.). 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. 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 modafinil for three weeks, a washout period of one week, and an open label extension of eight weeks, also reported decreased fatigue and improvements in cognitive functioning and mood in PBT patients, although final results have not been published yet. 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.

**METHODS**

**Participants**

We identified patients who visited the outpatient departments of three 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: 1) were ≥ 18 years old, 2) had been diagnosed with a histologically confirmed glioma or meningioma (collectively called primary brain tumor (PBT) throughout this report); and 3) had no signs of tumor recurrence in the last six months. In addition, they were only invited to participate if they reported a heightened experience of fatigue (score >27 on the Checklist Individual Strength (CIS), as this was our primary outcome measure. Patients were excluded if 1) they had a history of psychiatric disease or symptoms, including depressive disorders; 2) adverse interactions between modafinil and other prescribed medications were expected (e.g., decreased effectiveness of oral contraceptives, levonorgestrel-releasing intrauterine systems and anti-depressants, fluctuations in the effectiveness of anti-epileptic drugs acting on similar enzymes); 3) 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 α=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
participation. 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 randomisation 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 six 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 one, a washout period of one week was applied. Hereafter, the opposite treatment was provided during treatment period two (i.e., 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 one (after six weeks; T2) and immediately after treatment period two (after twelve weeks; 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). Fatigue was assessed with this multidimensional scale, each item scored on a seven-point Likert scale. The CIS includes four 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 Epidemiological Studies Depression Scale (CES-D). This 20-item questionnaire was used to assess symptoms of depression. Participants were asked to indicate, on a four-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 are considered depressed.

MOS Short-Form Health Survey (SF-36). This HRQOL survey is composed of 36 items that are organized into eight multi-item scales assessing: (1) physical functioning; (2) limitations in role functioning due to physical problems; (3) limitations in role functioning due to emotional problems; (4) pain; (5) vitality; (6) social functioning; (7) mental health; and (8) general health perceptions. From these scales, two higher-order summary scores can be calculated: 1) Physical Component Summary (PCS), measuring physical health; 2) Mental Component Summary
(MCS), measuring mental health. In a normative sample from the general population, PCS and MCS scores had a mean of 50 with a standard deviation of 10.

*MOS Subjective cognitive functioning scale.*190 This six-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), working memory (memory comparison test), attentional functioning (Stroop color word test), information processing (letter digit substitution test), executive functioning (concept shifting test, categorical word fluency test), 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 standard deviations of the patients’ scores at baseline. To achieve data reduction, six cognitive domains were formed (verbal memory; working memory; attentional functioning; information processing; executive functioning; psychomotor speed), see 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.193 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 ≤0.05 was considered statistically significant, a p-value of ≤ 0.10 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 patients (25.2%) 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 two patients dropped out before randomization because they were no longer willing to participate. During the trial, overall 12 patients dropped
out: seven participants dropped out between T1 and T2, and five patients 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 fatigue severity and reduced motivation were significantly lower after both modafinil ($p=0.010$ and $p=0.021$, respectively) and placebo treatment ($p<0.001$ and $p=0.027$, respectively) compared with the baseline assessment. The extent of decrease in fatigue as measured by these scales, however, did not significantly differ between

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**Figure 1.** Participant flow.
# Table 1. Demographic and clinical characteristics of the study sample.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants (N= 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years M (SD)</td>
<td>48.16 (12.02)</td>
</tr>
<tr>
<td>Gender N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (37.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (62.2%)</td>
</tr>
<tr>
<td>Educational level N (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Medium</td>
<td>15 (40.5%)</td>
</tr>
<tr>
<td>High</td>
<td>11 (29.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Marital status N (%)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Married or living together</td>
<td>25 (67.6%)</td>
</tr>
<tr>
<td>Divorced</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Widow(er)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Tumor grade N (%)</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>15 (40.5%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>10 (27.0%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Tumor type N (%)</td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td>12 (32.4%)</td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>14 (37.8%)</td>
</tr>
<tr>
<td>High-grade glioma</td>
<td>11 (29.7%)</td>
</tr>
<tr>
<td>Tumor location N (%)</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>13 (35.1%)</td>
</tr>
<tr>
<td>Temporal</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Parietal</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>Occipital</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Tumor lateralisation N (%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>15 (40.5%)</td>
</tr>
<tr>
<td>Right</td>
<td>20 (54.1%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Epilepsy N (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (32.4%)</td>
</tr>
<tr>
<td>No</td>
<td>25 (67.6%)</td>
</tr>
<tr>
<td>Neurosurgical intervention N (%)</td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>33 (89.2%)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>None</td>
<td>2 (5.4%)</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Months since time of diagnosis M (range)</th>
<th>Participants (N= 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 36 months N(%)</td>
<td>18 (48.6%)</td>
</tr>
<tr>
<td>&gt; 36 months N(%)</td>
<td>19 (51.4%)</td>
</tr>
</tbody>
</table>

Medication use, prior to trial N (%)

<table>
<thead>
<tr>
<th>Medication</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-epileptic drugs</td>
<td>20 (54.1%)</td>
</tr>
<tr>
<td>Anti-hypertensive drugs</td>
<td>8 (21.6%)</td>
</tr>
<tr>
<td>Cholesterol inhibitors</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Analgesics (mild opioids)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Analgesics (non-opioids)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Anti-allergic drugs</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Bladder control drugs</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Stomach protectors</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Laxatives</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Anorexiant</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Progestagens</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>1 (2.7%)</td>
</tr>
</tbody>
</table>

Change in medication use during trial N (%)

<table>
<thead>
<tr>
<th>Medication</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics (non-opioids)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Flue vaccine</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Anti-diabetics</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Anti-emetics</td>
<td>1 (2.7%)</td>
</tr>
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Radiotherapy (ever) N (%)

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>N(%)</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>16 (43.2%)*</td>
</tr>
<tr>
<td>No</td>
<td>21 (56.8%)</td>
</tr>
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</table>

Chemotherapy (ever) N (%)

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8 (21.6%)*</td>
</tr>
<tr>
<td>No</td>
<td>29 (78.4%)</td>
</tr>
</tbody>
</table>

Progressive disease during intervention N (%)

<table>
<thead>
<tr>
<th>Progressive disease</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>No</td>
<td>35 (94.6%)</td>
</tr>
</tbody>
</table>

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

Both conditions. Although not statistically significant, a trend can be seen for an improvement in reduced activity in the placebo condition (p=0.093) compared with baseline. On the total CIS-score, patients’ symptoms were alleviated in both the modafinil and placebo condition (p=0.005 and p=0.001, respectively) while scores between the experimental conditions did not differ.
Modafinil for symptom management in brain tumor patients

2.3

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 condition ($M=14.16$, $sd=9.06$ and $M=13.97$, $sd=9.44$, respectively; $p = n.s.$). All mean scores were within the non-depressed range (i.e. $< 16$).

Health-related quality of life

Patients’ physical health as measured by the PCS scale improved significantly after both the modafinil ($M=46.05$, $sd=7.96$) and placebo condition ($M=44.71$, $sd=9.13$) compared with baseline ($M=40.60$, $sd=7.58$; $p=0.001$ and $p=0.008$, 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 cognitive functioning after the placebo condition compared with baseline ($p=0.056$), see Table 3.

Objective cognitive functioning

Table 3 shows that patients improved after both the modafinil and the placebo condition compared with baseline for both the working memory domain ($p=0.040$ and $p=0.043$, respectively) and the information processing domain ($p=0.036$ and $p=0.040$, respectively). Scores did not differ between the experimental conditions. For attentional functioning, scores improved significantly after the placebo condition compared with baseline ($p=0.015$) and after modafinil treatment ($p=0.013$).

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

<table>
<thead>
<tr>
<th></th>
<th>Bas $N=36$</th>
<th>Mod $N=26$</th>
<th>Pla $N=29$</th>
<th>Bas vs. Mod</th>
<th>Bas vs. Pla</th>
<th>Mod vs. Pla</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M (sd)$</td>
<td>$M (sd)$</td>
<td>$M (sd)$</td>
<td>$Z (p)$</td>
<td>$Z (p)$</td>
<td>$Z (p)$</td>
</tr>
<tr>
<td>Concentration problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$20.75 (9.18)$</td>
<td>18.85 (7.90)</td>
<td>19.91 (8.36)</td>
<td>-1.10 (0.270)</td>
<td>-1.15 (0.252)</td>
<td>-0.97 (0.331)</td>
<td></td>
</tr>
<tr>
<td>Reduced motivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$17.00 (5.40)$</td>
<td>14.38 (5.72)</td>
<td>14.86 (6.72)</td>
<td>-2.31 (0.021*)</td>
<td>-2.22 (0.027*)</td>
<td>-0.383 (0.702)</td>
<td></td>
</tr>
<tr>
<td>Reduced activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13.49 (4.87)$</td>
<td>11.58 (5.34)</td>
<td>12.59 (5.17)</td>
<td>-1.37 (0.170)</td>
<td>-1.68 (0.093)</td>
<td>-0.43 (0.671)</td>
<td></td>
</tr>
<tr>
<td>Fatigue severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$41.72 (9.22)$</td>
<td>34.92 (12.04)</td>
<td>35.14 (10.86)</td>
<td>-2.56 (0.010*)</td>
<td>-3.72 (&lt;0.001*)</td>
<td>-0.75 (0.456)</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$93.80 (20.16)$</td>
<td>79.73 (26.45)</td>
<td>82.48 (26.26)</td>
<td>-2.83 (0.005*)</td>
<td>-3.35 (0.001*)</td>
<td>-1.01 (0.313)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Bas. baseline; Mod. modafinil; Pla. placebo.
* $p<0.05$
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 to 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 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. 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, two studies have been reported and both showed positive results. Gehring et al. 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. mention improvement in fatigue, mood and cognitive functioning in PBT patients randomized to either a 200mg or a 400mg 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, 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 Figure 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 includes 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, 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 (e.g., 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 homogenous 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 pharmacological trials for symptom management, as is shown in the present study as well as in the study by Gehring et al., 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 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 (e.g., 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. For depressive symptoms, nonpharmacological intervention studies in this patient population are also still scarce, although many therapeutic interventions already exist for different cancer patient populations. 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.

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