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Modafinil for attentional and psychomotor dysfunction in advanced cancer: a double-blind, randomised, cross-over trial

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Abstract

Cognitive impairment seems to be highly prevalent in patients with advanced cancer. Modafinil, a novel vigilance and wake-promoting agent, may be an alternative treatment. We wanted to investigate this treatment on attentional and psychomotor dysfunction in cancer patients. 28 cancer patients with a tiredness score of 50 mm or more on a scale of 0 to 10 (0 = no tiredness, 10 = worst possible tiredness) and Karnofsky Performance Status 40–70 were included. All medications were kept stable during the trial despite short acting opioids for breakthrough pain. On day 1 the patients were randomly assigned to receive 200 mg Modafinil orally or placebo and on day 4 they crossed-over to the alternative treatment. Finger Tapping Test (FTT), Trail Making Test (TMT) and Edmonton Symptom Assessment System (ESAS) were evaluated before tablet intake and again 4, 5 hours after. FTT for the dominant hand as well as TMT were statistically significantly improved on modafinil (p-values = 0.006 and 0.042, respectively). On ESAS, depression and drowsiness also improved statistically significantly (p-values = <0.001 and 0.038, respectively). Modafinil in a single dose regimen was significantly superior to placebo regarding two cognitive tests of psychomotor speed and attention. Furthermore subjective scores of depression and drowsiness were significantly improved by modafinil.

Key words

cancer, cognition, modafinil, neuropsychological assessment and symptoms

Introduction

Cognitive dysfunction is prevalent and serious in patients with advanced cancer. In palliative care using the Mini-Mental State Examination (MMSE), a study by Pereira et al.[1] comprising 348 inpatients showed a prevalence of cognitive dysfunction of 44% on admission, whereas 68% had abnormal MMSE scores before death. The multi-system impairment that accompanies progression of the cancer disease is undoubtedly associated with an increase in vulnerability towards cognitive impairment, which in the late stages of the disease may be manifested as delirium.[2]

Just like the symptom 'pain' received inadequate attention from cancer clinicians in the past, other symptoms than pain are often under-assessed and under-treated nowadays. Symptoms, such as cancer-related cognitive dysfunction, fatigue, sedation and drowsiness, seem to be highly prevalent and have only recently received attention by clinicians and researchers.[3] However, research in their epidemiology and mechanisms is still in its infancy, and therefore, treatments are not yet targeted due to lack of accurate classification and specificity of treatments.

Psychostimulants may offer new possibilities in managing symptoms related to cancer or its treatment. Modafinil, a novel vigilance and wake-promoting agent, may be potentially effective in cancer-related cognitive dysfunction, fatigue and opioid-induced sedation. Following oral administration, modafinil is rapidly and completely absorbed from the gastrointestinal tract and achieves peak plasma levels in 2–4 h. The elimination half-life after a single dose is between

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10 and 13 h.[4] Although various neurotransmitters have been proposed to be involved in the actions of modafinil, little is known about the molecular mechanisms by which modafinil increases wakefulness. It is likely that modafinil selectively enhances catecholaminergic signalling in the central nervous system (CNS) like amphetamine derivatives; however, modafinil acts primarily in the anterior hypothalamus, an area specifically involved in regulation of sleep architecture, whereas amphetamine derivatives generally act throughout the striatum and cortex.[5–8] Thus, modafinil interacts more with sleep-wake cycle rather than inducing generalised excitation, which may be responsible for its relatively low incidence of side effects and abuse potential. Results from open-label studies investigating the efficacy of modafinil in fatigue originating from multiple sclerosis and fibromyalgia and in opioid-induced sedation in non-malignant pain patients have encouraged for further studies in cancer patients.[9–11] Furthermore, controlled studies in patients suffering from narcolepsy, schizophrenia and major depression have also demonstrated improved cognitive function after modafinil administration.[12–14] However, to our knowledge, only two studies concerning modafinil in cancer patients are currently available as abstracts. In an open-label study in breast cancer patients, modafinil reduced fatigue, and in a randomised controlled study in patients with brain tumours treated with neurosurgical resection, radiotherapy and/or chemotherapy, modafinil reduced fatigue and improved activity, mood and cognitive functions.[15,16] Taken together, these findings justify a study of modafinil in patients with advanced cancer in palliative care.

The primary aim of this study was to assess the effectiveness of a single-dose modafinil versus placebo on cognitive function in patients with advanced cancer treated in palliative care settings. The secondary aim was to assess the effectiveness of modafinil on other symptoms.

Material and methods

Patients

Thirty-six patients with advanced cancer were approached by the homecare team of the Department of Palliative Care, Herning Hospital. The ethics committee and the Danish Medicines Agency approved the protocol, and written informed consent was obtained from all patients. Twenty-eight patients with advanced cancer were recruited for the study. Patient characteristics are summarised in Table 1. Inclusion criteria were age >18 years, tiredness score >50 mm on the Edmonton Symptom Assessment System (ESAS), Karnofsky performance status (KPS) 40–70%, a hemoglobin level of at least 6.5 mmol/l, creatinine <150 mmol/l and total S-calcium <2.7 mmol/l. All medications were kept stable 1 week before and during the trial; however, the patients were allowed to use supplemental doses of short-acting opioids for breakthrough pain throughout the study except before testing on the study days.

Table 1. Demographics, primary cancer disease and performance status

Characteristic	Total ($N = 28$)
Age, years	
Median	62
Range	40–79
Sex	
Male	16
Female	12
Primary cancer site	
Breast	1
Genitourinary	6
Gastrointestinal	5
Head/neck	2
Hematologic	1
Lung	9
Other	4
Karnofsky performance status	
Median	70
Range	50–70

Exclusion criteria were the following: women who were pregnant or lactating and patients with a history of severe anxiety disorders, significant arterial hypertension or untreated tachycardia, CNS metastases, significant hepatic or renal dysfunction, administration of ethinylestradiol, triazolam and monoamine oxidase inhibitors. Patients were not allowed to use methylphenidate or to start corticosteroids within 2 weeks of enrolment in the study. However, patients on low-dose methylprednisolone (methylprednisolone <25 mg/day) were allowed to continue.

Methods

The study design was a double-blind, randomised, cross-over, single-dose trial. On day 1 between 8 and 10 a.m., patients were randomly assigned to receive 200-mg modafinil or placebo orally, and on day 4 between 8 and 10 a.m., they were crossed-over to the alternative treatment. The randomisation procedure was organised by the hospital pharmacist using a computerised program. Restricted and balanced randomisation was used with eight patients in four blocks, as dropouts were expected. Blinded to the members of the

research team, the pharmacist prepared the study medication for day 1 and day 4. The pharmacist did not meet any of the patients.

All assessments were carried out in the patients' homes by two trained investigators (LEL and BHJ.) in a standardised way. Testing was performed with the patients in sitting position. Finger Tapping Test (FTT), Trial Making Test B (TMT) and ESAS were evaluated before tablet intake and again 4.5 h after. Before administration of the drugs, the test battery was presented to the patients to ensure familiarity with the tests and to minimise practice effects throughout the day. The testing procedure lasted approximately 400 min and was administered in the order mentioned above. Furthermore, sleeping problems and side effects were registered.

The FTT is a well-validated test of psychomotor speed used for detecting lateral cerebral lesions but also for detecting unspecific psychomotor impairment. The test demanded the patient to tap a key as fast as possible. The key is attached to a device measuring the number of taps. The second finger of each hand (dominant and non-dominant) made five 10-s trials with brief resting periods between the trials (<10 s). The score was given as the average number of taps for each of the five trials.[17] Test–retest reliability coefficients for the dominant and non-dominant hands have been shown to be high (about 0.8).[18] Criterion validity has been demonstrated in studies differentiating between patients with and without cerebral affection by both intra- and inter-individual comparisons.[19,20] Concurrent validity has been demonstrated through associations between the test and the electroencephalogram and magnetic resonance imaging findings.[19,21] Both age and gender exert effects on FTT, as men consistently tap faster than women. Slowing with age becomes prominent from the fifth decade with greater decrements through the subsequent decades. Education has negligible influence on FTT.[18,22] The test has formerly been used for assessment of cancer-related cognitive impairment.[23]

The TMT is a test of visual information processing involving visual search, scanning, speed of processing, mental flexibility, attention and psychomotor speed. There exist two forms of TMT (form A and B); however, only trail B was used in this study. The patient was instructed to draw connecting lines between consecutively numbered and lettered circles by alternating between the two sequences. The patient should complete the test as quick and accurate as possible without lifting the pen from the paper. If an error was made, the patient was instructed to return to the 'circle' from where the error originated and continue. Time for completion of the test was recorded in seconds. A higher score is indicative of poorer performance. There exists an extensive normal material, and the test is well validated. TMT tends to decline with advancing age, and some practice effects have been reported to affect test results (5% difference) after a 3-week period.[24–26] TMT has recently been used to assess opioid-induced cognitive dysfunction.[27]

Multiple symptoms before and after the two treatments were assessed using ESAS. This tool is designed to assess nine symptoms common in cancer patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath (there is also a free scale labelled 'other problems'. In this study, constipation was chosen). The severity of each symptom is rated from 0 to 10 on a numerical scale; 0 means that the symptom is absent and 10 means that it is of the worst possible severity. In this study only, patients themselves filled in the ESAS. This assessment scale has formerly been validated in cancer patients.[28]

The KPS scale is a validated observer measure that is widely used in the clinical trials in cancer patients.[29] In cancer research, it has been used as a patient stratification criterion and as an outcome measure for treatment efficacy.[30] The score ranges from 100 to 0% and reflects a combination of disease status, independence and role functioning; 100% is 'normal, no complaints and no evidence of disease' and 0% is 'dead'.[31]

Patients' sleep was assessed quantitatively as the number of sleeping hours per night and qualitatively by asking open-ended questions regarding excessive dreams, difficulty in falling asleep, interrupted sleep and waking up early. The sleep was assessed from the night before study start until three nights after intake of the second tablet.

A side-effect recording sheet was administrated 24 h after both treatments. It included the well-known side effects for modafinil such as nausea, headache, restlessness, anxiety and diarrhoea. The patients were asked to rate each of the potential side effects as none, slight, moderate or severe.

The patients' concurrent medications were recorded throughout the study period.

Statistics

The number of patients included in the study was determined by statistical power calculations and based on previous findings in the literature assuming that modafinil (200 mg daily) may have effects of the same magnitude as methylphenidate (15 mg daily).[32] This indicated that a sample size of $N = 28$ would insure sufficient statistical power to detect relevant clinical differences in change: it would result in a power of about 95% to detect a difference of 20 on a 100-mm visual analogue scale of drowsiness and a power of about 85% to detect a difference of 15 mm.

To evaluate the effect of modafinil compared with placebo, we calculated the change from before treatment (baseline) to after treatment for each variable and then calculated the difference in these changes for modafinil and placebo, respectively. The Wilcoxon signed-rank test was used to test these differences in change. The general level of significance was set at $P < 0.05$. All analyses were carried out using the SAS statistical software package v. 9.1.3.[33]

Results

Between April 2005 and July 2007, a total of 36 patients were found eligible and were approached in their homes for inclusion in the study. Three patients were withdrawn from the study before study start because of progression of the disease resulting in KPS <40 mm, one patient was included in another study contemporarily, and two patients refused to participate. Thus, 30 patients consented and underwent random assignment (Figure 1). During the study, two patients dropped out due to progression of disease. Demographics of the 28 participating patients are summarised in Table 1. There were no statistically significant differences between the two study arms regarding demographics, primary cancer disease and performance status at baseline assessment. The patients' concurrent medications are listed in Table 2.

FTT with the dominant hand and TMT were statistically significantly improved on modafinil treatment compared with placebo (P values = 0.006 and 0.042, respectively).

Table 3 shows the mean difference in symptom intensity after treatment between modafinil and placebo measured by ESAS. Depression and drowsiness were statistically significantly improved on modafinil treatment compared with placebo (P values = 0.001 and 0.038, respectively).

Table 4 dispels the differences in hours of sleep night 1 to 3 after modafinil and placebo treatment, respectively. There were no statistically significant differences between the two treatments. Regarding quality of sleep, four patients experienced disrupted sleep and vivid dreams after modafinil treatment.

The frequency and intensity of side effects were similar on both treatments, and there were no statistically significant differences.

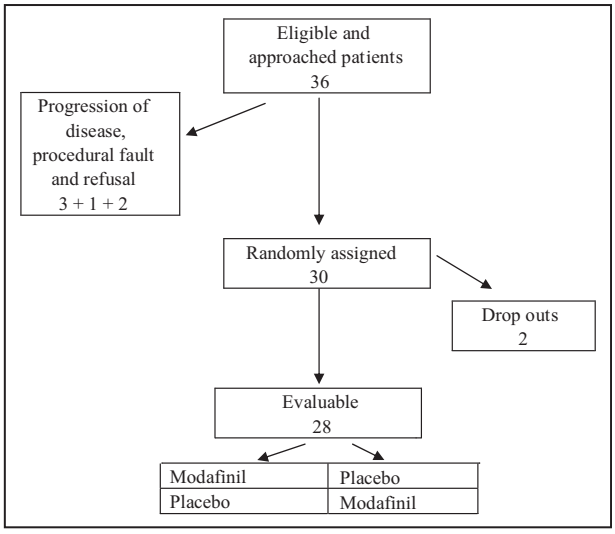

Figure 1. Flow diagram.

Table 2. Medications used by the 28 participating patients (excluding short-acting opioids given on demand for breakthrough pain)

Type of medication		Number of patients	Median (dose/day)	Range (dose/day)
Opioids	Morphine SR	3	80 mg	40–120 mg
	Oxycodon SR	9	140 mg	30–320 mg
	Fentanyl TD	15	75 μg/h	37.5–300 μg/h
	Methadone	4	62.5 mg	60–70 mg
Benzodiazepines	Zopiclone	8	7.5 mg	7.5 mg
	Oxazepam	8	12.5 mg	5–30 mg
Antidepressants	Amitriptyline	7	25 mg	10–50 mg
	Nortriptyline	2	20 mg	20 mg
	Citalopram	2	30 mg	20–40 mg
	Other SSRIs	3	—	—
Anticonvulsants	Pregabaline	6	175 mg	50–300 mg
NSAIDs		3	—	—
Methylprednisolone		11	25 mg	7.5–25 mg
Paracetamol		13	3 g	2–4 g

SR, sustained release; TD, transdermal; NSAIDS, non steroidal anti-inflammatory drugs.

Two of the patients did not return the recording sheet after the second treatment phase, which explains the sample difference of the two groups (Table 5).

Table 3. Differences in scores for symptom intensity by ESAS between modafinil and placebo treatment ($N = 28$)

Symptom	Mean	SD	*P* value
Pain	−0.071	2.035	0.863
Fatigue	−0.857	2.953	0.111
Nausea	−0.286	0.854	0.138
Depression	−1.071	1.538	<0.001*
Anxiety	0.250	2.012	0.672
Drowsiness	−1.357	3.423	0.038*
Shortness of breath	−0.571	2.098	0.089
Appetite	−0.607	3.071	0.398
Feeling of well-being	−1.214	3.489	0.069
Constipation	0.037	2.139	0.874

ESAS, Edmonton Symptom Assessment System.
*Statistically significant values.

Table 4. Sleep assessment

	Mean	SD	*P* value
First night after treatment	−0.44	2.50	0.152
Second night after treatment	0.48	2.02	0.267
Third night after treatment	0.52	2.62	0.285

Differences in sleeping hours night 1 to 3 after modafinil and placebo treatment ($N = 28$).

Discussion

Cancer diseases and anticancer treatments are accompanied by various severe and prevalent symptoms, which diminish quality of life of the patients, and are usually difficult to combat. These include cognitive dysfunction, fatigue, sedation, drowsiness and mood disturbances. Psychostimulants offer new possibilities in managing these symptoms, and out of the three 'classical' psychostimulants, (amphetamine, methylphenidate and pemoline) methylphenidate had been most thoroughly assessed in cancer patients.[32,34,35] Because amphetamine is feared for its abuse potential and pemoline production has been stopped, methylphenidate remains the 'gold-standard' psychostimulant, which seems to have a future potential in palliative and supportive treatment of cancer patients. However, the lower abuse potential and more specific effects seem to be an advantage of modafinil, when comparing it to methylphenidate. In addition, tolerance development seems to be lesser with modafinil than with methylphenidate, which makes modafinil a potential treatment option in earlier stages of cancer diseases and in cancer survivors.[36,37]

Currently, modafinil has been tested for persistent fatigue in patients who completed breast cancer treatment.[15] In an open-label study, 51 patients received 200-mg modafinil in the morning. Fatigue severity level was measured using 0–10 scale, where 0 = 'not present' and 10 = 'as bad as you can imagine'. The mean fatigue severity level was reduced statistically significant. Furthermore, the majority of patients reported improvement in general activity, mood and normal

Table 5. The frequency and intensity of side effects

Side effects	No. of patients	%	Slight	Moderate	Severe
Modafinil treatment ($N = 26$)					
Nausea	8	30	4	3	1
Headache	6	23	3	0	3
Restlessness	7	27	4	1	2
Anxiety	3	12	1	1	1
Diarrhoea	3	12	2	1	0
Others	None	None	None	None	None
Placebo treatment ($N = 28$)					
Nausea	12	43	6	5	1
Headache	4	14	3	0	1
Restlessness	8	29	3	3	2
Anxiety	9	32	6	1	2
Diarrhoea	4	14	2	1	1
Others	None	None	None	None	None

work ability. Patient reported global effectiveness of modafinil was mean 5.0 during this study (1 = 'no benefit' and 7 = 'great improvement'). The only currently available randomised study assessing effects of modafinil regarding cognition and fatigue was presented in 2006 at the Annual ASCO Meeting.[16] The study involved 30 patients with brain tumours treated with neurosurgical resection, radiotherapy and/or chemotherapy. Cognitive dysfunction and depression were assessed using TMT A and B, Symbol Digit Modalities, Verbal Fluency and Hamilton Depression Scale. Fatigue was measured with Fatigue Severity Scale, Visuals Analogue Fatigue Scale and Modified Fatigue Impact Scale. Patients were randomised in the double-blind, dose-controlled design to receive 200- or 400-mg modafinil daily for 3 weeks. After 1-week washout, the study was continued for 8 weeks in an open-label fashion. Statistically significant improvement in all measured parameters was observed with greatest improvement 8 weeks after baseline. In these trials, especially mood, activity, fatigue and cognition were improved, and corresponding to our results the latter trial convincingly showed that different domains of cognitive function improved significantly following administration of modafinil.

In patients with advanced cancer, cognitive disorders are among the most frequent symptoms, and its prevalence ranges from 10 to 90% depending on assessment tools used and populations studied.[38–41] These cognitive disorders may be ascribed to a variety of causes, which according to aetiology can be classified in three main categories: disease-related causes, treatment-related causes and causes-related to other factors.[42–44] In this study, the gross cognitive effects of causes from all categories were measured in specific domains (FTT and TMT), although some of the causes were excluded by the exclusion criteria. However, it is noteworthy that no consensus is yet established concerning neuropsychological assessment of cognition in cancer patients, although most neuropsychological assessment have been engaged in domains of attention, psychomotor speed, information processing speed and short-term memory.[23,45–47] The precision and sensitivity of neuropsychological measurement techniques make them valuable and attractive instruments for investigating even small and subtle behavioural alterations. However, patients' complaints of cognitive deficits cannot be directly associated with objective measures of cognitive function, and the cognitive deficits detected by neuropsychological testing cannot readily be 'translated' into everyday tasks such as car driving, operating machinery, looking after children, etc. Furthermore, the influence of cognitive dysfunction on quality of life is virtually unknown.[48] Finally, the concept of 'symptom clusters' referring to the concomitance of symptoms, which are related to each other in a logical or predictable way, may also play a role in cognitive dysfunction.[49] For instance fatigue, sedation, drowsiness, mood disturbances, cognitive dysfunction and other symptoms may interact with each other and may individually, or as clusters, be responsive to treatments. Therefore, the importance of unpacking aetiologies of cognitive dysfunction is obvious, as reversibility makes some of them manageable. Detection of cognitive dysfunction in the early stages of the cancer disease may have important implications for predicting more severe cognitive failure and even delirium in the later stages and may indeed have implications for more specific interventions based on aetiology.

Interestingly, the two abstracts concerning modafinil in cancer patients demonstrated – also in line with our findings – that mood improved significantly.[15,16] Fast onset of the antidepressant effect of psychostimulants (within days) has formerly been indicated in smaller open-label studies in patients with advanced cancer receiving methylphenidate.[50,51] Likewise, modafinil seems to have these effects, which are of great importance for patients in palliative care, as they cannot await weeks or months for the slow onset of the traditional antidepressants.[14,52,53] Depression is frequently met in cancer patients in palliative care[41]; however, the role of modafinil and other psychostimulants as antidepressants needs to be studied in more depth in this population. Another interesting finding in our study was that modafinil did not induce anxiety measured by the ESAS and side-effect records. Studies on modafinil in healthy volunteers and patients with multiple sclerosis have formerly demonstrated increased anxiety scores on different assessment tools compared with placebo.[54,55]

In this study, drowsiness measured by ESAS was reduced statistically significantly compared with placebo. Surprisingly, modafinil did not improve tiredness significantly despite the fact that a high score on this scale served as an inclusion criterion (tiredness > 50 mm). However, symptoms such as drowsiness and tiredness may be difficult to distinguish for patients with advanced cancer.

There were no statistically significant differences between patients receiving modafinil versus those receiving placebo regarding side effects and sleeping problems. Modafinil may have an advantageous side-effect profile compared with methylphenidate; however, at higher dose levels, both side effects and sleep disturbances may likely appear.[56] Furthermore, this study may not be powered to detect differences in side effects and sleep disturbances.

Conclusion

Psychostimulants are becoming increasingly important as pharmacological options in the treatment of cognitive dysfunction, fatigue, drowsiness, sedation and depression in patients with advanced cancer. In patients with advanced cancer, this study demonstrated that modafinil improved attention and psychomotor speed significantly compared with placebo in a single-dose study. Furthermore, subjective scores of depression and drowsiness were significantly improved after modafinil compared with placebo. At the chosen dose level, no side effects or significant sleeping problems were registered after modafinil compared with placebo.

Our findings suggest that modafinil counteracts in cancer-related cognitive dysfunction; however, long-term studies as well as dose finding studies are needed to further evaluate its clinical usefulness.

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