

Modafinil for the Treatment of Daytime Sleepiness in Parkinson's Disease: A Double-blind, Randomized, Crossover, Placebo-controlled Polygraphic Trial

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Objectives: To assess the therapeutic efficacy of modafinil in the treatment of increased daytime sleepiness in patients with Parkinson's disease (PD).

Design: Double-blind, randomized, placebo-controlled crossover study with two 2-week treatment blocks, separated by a 2-week washout phase.

Setting: Tertiary Parkinson's disease care center and sleep laboratory at university hospital neurology department.

Patients: Fifteen patients with idiopathic PD and daytime sleepiness (Epworth sleepiness score (ESS) 10 or more)

Interventions: Administration of placebo or modafinil as a single morning dose in a randomized crossover order. The modafinil dose was 100 mg in the first, and 200 mg in the second treatment week.

Measurements and Results: At baseline and at the end of each treatment block, sleepiness was evaluated using subjective (perceived sleepiness with the ESS) and objective measures (maintenance of wakefulness

test). Twelve patients completed the study (9 male, 3 female; mean age 65.0 ± 7.6 years, mean disease duration 6.8 ± 4.1 years). Epworth scores were significantly improved with modafinil (3.42 ± 3.90) compared to placebo (0.83 ± 1.99 ; $p = 0.011$). Latency to sleep in the maintenance of wakefulness test was not significantly altered by modafinil treatment: 10.9 (3-40) / 15.1 (2.5-40) minutes before/after placebo and 12 (2.6-40) / 17.8 (4.2-40) minutes before/after modafinil ($p = 0.139$) [data given as mean \pm standard deviation or median (range)].

Conclusions: The results of this study suggest that modafinil improves daytime sleepiness in PD patients, at least on a subjective or behavioral level. Modafinil treatment may be considered for EDS in PD patients, in whom otherwise treatable causes of Excessive Daytime Sleepiness (EDS) are absent.

Key Words: Sleepiness - sleep - Parkinson's disease - polysomnography - Epworth sleepiness scale - maintenance of wakefulness test - modafinil

INTRODUCTION

EXCESSIVE DAYTIME SLEEPINESS (EDS) IS INCREASINGLY RECOGNIZED AS MAJOR PROBLEM IN PARKINSON'S DISEASE (PD).^{1,2} Night sleep disruption,³ comorbidity,⁴ dopaminergic therapy,^{5,6} and nondopaminergic therapy⁴ all contribute to EDS. Moreover, the sleep-wake disturbances seem to relate to dopamine deficiency in PD,^{1,2,4} and a narcolepsy-like phenotype has been described in a subgroup of patients.^{7,8} A few case reports deal with treatment,⁹⁻¹¹ but controlled polygraphic studies are lacking.

We conducted the present study to evaluate the effect of modafinil treatment on subjective and objective measures of sleepiness in patients with PD.

METHODS

Screening

Participants of this study were recruited from the PD outpatient clinic at the University Hospital Department of Neurology in Innsbruck, Austria. Patients were selected on the basis of daytime sleepiness established by means of the Epworth sleepiness scale (ESS)¹² and all patients with a score of 10 or more were eligible.

Disclosure Statement

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Recruitment

All patients with an ESS 10 or more were invited for a recruitment visit. At this visit, the purpose of the study was explained, the ESS was administered again, a sleep history was taken, and inclusion and exclusion criteria checked. Before study entry, patients underwent ambulatory screening for sleep-related breathing disorders. The screening device (MESAM IV, MAP Germany) consisted of sensors for percutaneous oxygen saturation, heart rate, body position, and snoring. It fulfilled the criteria for devices to detect sleep-disordered breathing established by the Task Force of the American Academy of Sleep Medicine.¹³ If exclusion criteria were absent and informed consent was given, randomization was performed.

Inclusion and exclusion criteria

Inclusion criteria were idiopathic PD according to the United Kingdom Parkinson's Disease Society brain bank criteria,¹⁴ subjective complaint of EDS, and ESS score of 10 or more.

Patients with an age over 80, atypical PD (multisystem atrophy, progressive supranuclear palsy, Lewy body dementia or drug-induced parkinsonism according to established criteria), dementia (mini mental state < 25), current drug-induced psychosis, severe medical conditions that might interfere with night sleep or daytime sleepiness, or contraindications against modafinil (severe heart disease, hepatic cirrhosis, severe arterial hypertension, severe renal insufficiency) were excluded. Patients with sleep-disordered breathing treatable by nasal positive airway pressure (nCPAP) or bilevel positive airway pressure (BiPAP), a history suggestive of REM sleep behavior disorder (complex movements associated with dream content, or apparent dream enactment), regular use of hypnotics (> 15 mg/d diazepam equivalent) or irregular hypnotics use that could not be reliably stopped for the duration of the study were also excluded.

Study Design

The study was designed as a 6-week, double-blind, randomized, placebo-controlled trial. Two 2-week crossover treatment periods were separated by a 2-week washout phase. At the beginning and at the end of each treatment block, the following tests were performed: Maintenance of wakefulness test, ESS, sleep log for the previous night, and Beck depression scale.¹⁵ Severity of PD was assessed using the Unified Parkinson Disease Rating Scale (UPDRS) as well as the Hoehn and Yahr staging.¹⁶ At each study day, patients presented to the hospital between 8:00 and 9:00 am to prepare for polygraphic recording and questionnaires. Patients were asked to adhere to regular sleep-wake schedules during the study. Antiparkinsonian medication was kept stable throughout the study.

Randomization

Randomization was performed in the hospital's pharmacy. Two containers with medication were prepared for each patient, denominated with A (for the first treatment phase) and B (for the second treatment phase). A sealed envelope with the corresponding codes was kept in the pharmacy, and in the sleep laboratory for cases of emergency. The code was broken only after the end of the study.

Drug administration

Modafinil and placebo were prepared in identical-looking capsules. During the first week of treatment, one capsule and, during the second week, two capsules of the study medication were taken as a single dose together with the morning dose of antiparkinsonian medication.

Safety evaluation

At each study visit, side effects of treatment were checked and documented by one of the authors (MS).

Ethics

The protocol conformed to the declaration of Helsinki and had been previously approved by the University Hospital's ethics committee. All patients gave written informed consent before entering the study.

OUTCOME MEASURES

Epworth Sleepiness Scale

The ESS¹² is an 8-item questionnaire in which the probability to fall asleep is assessed for 8 different, everyday life situations. The majority of questions capture involuntary sleep episodes. Each answer is rated by the subject on a scale from 0 to 3 for "recent times." In our study, a slightly modified wording was used by replacing "recent times" by "the last two weeks," to be more specific and in accordance with the temporal design of the study. It was expected that this minor modification would not impair the generalizability of the data. The ESS has been shown to be sensitive to treatment effects.¹⁷

Maintenance of wakefulness test

To evaluate the effect of modafinil on the capacity to remain awake, the maintenance of wakefulness test (MWT) was performed using the standardized version described by Doghramji.¹⁸ Briefly, polygraphic sleep recording included EEG (C3, C4, O1, O2 according to the 10/20 system¹⁹) horizontal EOG, chin and submental EMG, and infrared video. Four runs with a duration of 40 minutes were performed at 10am, 12am, 2pm and 4pm. For each run, the patient was seated in a comfortable, slightly reclined chair, in a dark room, and was instructed to remain awake. When definite signs of sleep were observed for at least one epoch in the PSG, the trial was stopped. For later sleep latency determinations, the polygraphic recordings were analyzed according to standard

criteria²⁰ by an experienced sleep neurologist prior to unblinding of the study (EB). Sleep onset was defined as one 30-second epoch of Stage 1 sleep or any other sleep stage. One patient had subthalamic nucleus (STN) stimulation (monopolar mode). Because stimulation artifact could not be eliminated from online recording without changing stimulation parameters, this patient's MWT data were excluded.

Sleep Log and depression scale

In addition, to control for variable sleep-wake schedules and effects of sleep loss, patients kept a simple sleep log in which the estimated amount of sleep in the nights preceding the study evaluation days was documented. The Beck depression scale¹⁵ was also administered at each visit.

Statistics

Descriptive statistics included means \pm standard deviation for normally distributed data, and median \pm range for not normally distributed data. To test for normal distribution of data, Kolmogorow Smirnov Test with Lilliefors correction was used.

Data from ESS scores were normally distributed. An analysis of variance (repeated measures design) was performed with two within-subjects factors: placebo versus medication and baseline versus final evaluation of each treatment block. *t*-tests were performed to assess further differences between the time points. Data are summarized using mean \pm standard deviation and illustrated by bar chart (Figure 1).

No normal distribution could be assumed for the MWT. The nonparametric Friedman test and Wilcoxon test were used as appropriate. Data were summarized using medians and range. For MWT, sleep latencies were determined at 4 different time points (10 am, 12 am, 2 pm, 4 pm), and summarized as medians.

RESULTS

Patients

A population of 99 patients was screened. Thirty-three had an ESS Score of 10 or higher. Fifteen patients fulfilled all criteria and were included in the study. Three patients did not finish the study. One patient withdrew for intolerance of the MWT protocol (prolonged quiet sitting in a dark room) during the evaluation at the end of the first treatment block, which was placebo in his case. Another patient had to be excluded at the end of treatment block one for noncompliance with the protocol requirements (did not appear for scheduled visits, did not adhere to a regular sleep-wake schedule during the study). He had also received placebo treatment. One patient with cardiac arrhythmia and orthostatic hypotension experienced a presyncopal state while sitting in a chair for electrode positioning for baseline evaluations before administration of any study medication. This patient was excluded for his impaired global state and expected intolerance of prolonged sitting periods for electrode positioning and MWT involved in the protocol. As these 3 patients did not come to finish a whole evaluation block, their data were not included in further analyses.

Twelve patients completed the study. They were 9 men, 3 women; their mean age was 65.0 ± 7.6 years, and their mean symptomatic PD duration 6.8 ± 4.1 years). Median Hoehn and Yahr stage¹⁶ was 2.3 (2-4). During their participation in the study, their antiparkinsonian treatment consisted of levodopa ($n = 12$, 591 ± 219 mg/d), dopamine agonists (pergolide $n = 6$, 2.7 ± 0.8 mg/d, ropinirole $n = 2$, 3 mg/d, pramipexole $n = 1$, 1.1 mg/d), entacapone ($n = 2$, 600-800 mg/d), and amantadine ($n = 3$, 100-150 mg/d). Additional cotreatment included amitriptyline ($n = 3$, 25 mg/d), sertraline ($n = 1$, 50 mg/d), zolpidem ($n = 2$, 10 mg/d), verapamil ($n = 1$, 80 mg/d), lisinopril/hydrochlorothiazide ($n = 1$, 20/25 mg/d), acetylsalicylic acid ($n = 1$, 100 mg/d), levothyroxine ($n = 1$, 0.1 mg/d), pentoxifylline ($n = 1$, 400 mg/d), donepezil ($n = 1$, 10 mg/d). In 1 patient, moderate sleep-disordered breathing was detected, but specific

ic treatment was not applicable due to severe motor impairment impeding nCPAP or BiPAP handling.

Epworth sleepiness scores

Modafinil treatment led to an improvement of perceived sleepiness in the ESS as shown in Figure 1. The ESS scores at baseline did not differ between the treatment and the placebo block (11.8 ± 3.8 before placebo, 13.2 ± 2.2 before modafinil). Subjective sleepiness improved by 0.83 ± 1.99 points with placebo, and by 3.42 ± 3.90 with modafinil (mean ± sd). Analysis of variance revealed a significant interaction ($p = 0.011$) between medication condition and ESS score changes from baseline to end.

Maintenance of wakefulness tests

To evaluate the effects of modafinil on the capacity to stay awake, the latency to stage 1 sleep was calculated using the MWT. Due to exclusion of the patient with STN stimulation, data are based on 11 patients.

The latency to S1 sleep was 10.9 (3-40) minutes at the beginning of placebo treatment, 15.1 (2.5-40) minutes at the end of placebo treatment, 12 (2.6-40) minutes at the beginning of modafinil treatment, and 17.8 (4.2-40) minutes at the end of modafinil treatment. No significant differences were found in sleep latency between both conditions at baseline ($p = 0.26$), and at the end of the treatment phase ($p = 0.114$). The mean changes of sleep latencies at the end versus beginning of each block were also not significantly different. ($p = 0.139$).

Sleep Logs

Analysis of sleep logs for the night preceding each MWT showed that similar amounts of sleep were obtained in all conditions: Estimated time of sleep 390 ± 80 min at baseline of placebo treatment, 360 ± 94 min at the end of placebo treatment, 375 ± 86 min at baseline of modafinil treatment, and 360 ± 50 min at the end of modafinil treatment (median standard deviation, $p = 0.3$).

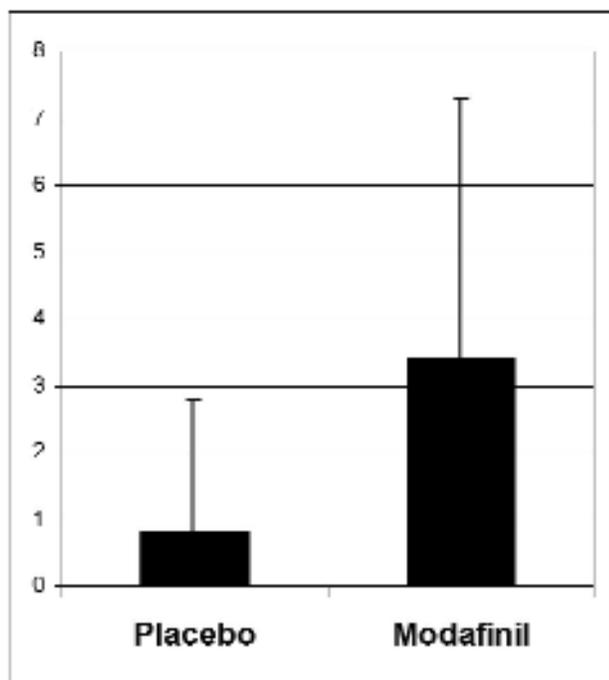


Figure 1—Epworth sleepiness scale: Improvements between baseline and end of treatment for placebo and modafinil. The differences in score changes were significant ($p = 0.011$). Means and standard deviation.

Depression Scores

Beck depression scores were 10.1 ± 7.3 at baseline of the placebo treatment, 9.4 ± 5.6 at the end of placebo treatment, 9.6 ± 6.9 at baseline of modafinil treatment, and 8.3 ± 6.7 at the end of modafinil treatment (mean ± standard deviation). These differences were not statistically significant.

Side effects

Side effects with modafinil were mild and included insomnia ($n = 1$), constipation ($n = 1$), diarrhea ($n = 2$), dizziness ($n = 1$). With placebo, the following side effects were reported: constipation ($n = 1$), flatulence ($n = 1$), diarrhea ($n = 1$), insomnia ($n = 1$). In no case did side effects lead to study withdrawal.

DISCUSSION

In this study, we evaluated the effect of modafinil for treatment of daytime sleepiness in PD patients. The ESS significantly improved with modafinil compared to placebo, whereas the MWT failed to show significant changes.

The ESS reflects behavioural sleepiness (the probability to fall asleep in eight situations differently conducive to sleep) as perceived by the patient and is, therefore, considered a subjective,²¹ although reliable¹⁷ measure. The MWT relies on electroencephalographic correlates of sleepiness (sleep latency) and is, therefore, generally accepted as an objective measure of sleepiness.

Although there is no universal acceptance of any specific cut-off score of the ESS to define clinically meaningful daytime sleepiness, most studies have chosen a pragmatic score of 10 for this purpose.²² Although lower cut-offs have been shown to be more closely associated with sleeping episodes at the wheel in PD patients,²³ a cut-off of 10 was chosen for this trial since we did not want to specifically select severely affected patients only. A high variability of ESS scores was present in this and the other studies.^{32,44} Previous studies found poor correlations between the ESS and polygraphic tests such as the multiple sleep latency test or the MWT,^{21,24,25} possibly because they measure different aspects of sleepiness.²⁴ There is an ongoing controversial discussion about which test is more valid.^{21,26-28} On the basis of this discussion, Sangal and coworkers have stressed the importance of not relying on either “subjective” or “objective” indices of sleepiness but to use both types of tests together in making clinical decisions.²⁴

Using the MWT rather than the MSLT as an objective measure for sleepiness in this study was based on two main reasons: First, the MWT measures the capacity to remain awake in a monotonous environment whereas the MSLT measures the propensity to fall asleep in a sleep-conducive environment. The capacity to remain awake was considered more relevant to PD patients, as monotonous situations occur in many everyday environments such as car driving. Second, the MWT has been said to be more sensitive to treatment effects than is the MSLT.¹⁸

The failure to detect any difference in sleep latencies between placebo and modafinil may relate to the fact that MWT data were not normally distributed and showed a great variation, ranging from 2 to 40 minutes in a 40-minute test session, which reduces the statistical power. A great variation ($7.1 ± 40$ min) of sleep latencies in the MWT has also been found in normals.²⁹ Moreover, sleep latency in the MWT probably does not reflect momentaneous sleepiness alone but is codetermined by genetic factors, as a genetic basis of sleep and wakefulness control is increasingly recognized.³⁰⁻³²

Several case reports have described successful modafinil treatment of daytime sleepiness in PD,⁹⁻¹¹ but it is difficult to draw conclusions about the therapeutic potential of modafinil in parkinsonian sleepiness from them.³³ However, two recent studies, one of them placebo-controlled,³⁴ have also reported ESS improvements with modafinil in PD.^{34,44} None of them included polygraphic data.

In the present study, only 15 out of 33 patients with an ESS score of

10 or more were included; the others lacked a subjective complaint of daytime sleepiness, were on higher-dose hypnotic treatment, or met other medical exclusion criteria. Therefore, caution should be used to generalize the results of this study to all patients with PD, and the indication and contraindications for modafinil treatment should be carefully considered in every patient.

The exact mode of action by which modafinil increases wakefulness is unclear. Noradrenergic,³⁵ alpha-adrenergic,³⁶ GABA-modulating,³⁷ and hypocretin/orexin stimulating/activating³⁸ mechanisms have been discussed, as well as activation of anterior hypothalamic and suprachiasmatic nuclei.³⁹ Recently, intravenous application of modafinil has been shown to increase extracellular dopamine in the caudate in narcoleptic dogs and DAT knockout mice did not have an increased wakefulness response to modafinil.⁴⁰ We do not know if dopamine transporter deficiency diminishes the magnitude of response to modafinil in PD patients, compared to other disorders of excessive daytime sleepiness such as narcolepsy. Given the induction of sleepiness by levodopa and dopamine agonists in patients with PD, a dopaminergic mechanism of modafinil in reducing sleepiness in PD would seem paradoxical, however.

Daytime sleepiness goes along with serious consequences such as increased risk of accidents,^{41,42} social handicap⁴³ and can seriously impair quality of life. Whereas motor function, mimic expression, and voice have all been recognized as major determinants of social function in PD patients, the importance of wakefulness has long been neglected outside the sleep community, or reduced to driving abilities. The capacity to sustain wakefulness however has outstanding importance for participation in social and family life.

The results of this study suggest that modafinil improves daytime sleepiness on a subjective or behavioral level in PD patients. Further studies will be necessary to determine if higher modafinil doses will show more marked effects and to collect data on the long-term clinical efficacy of modafinil in treating different forms of daytime sleepiness in PD.

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