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Original article

A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy

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Abstract

Objective: To assess the continued efficacy of modafinil in the treatment of excessive daytime somnolence (EDS) of narcolepsy.

Background: Modafinil has been shown to be a safe and effective treatment for the EDS presented by patients with narcolepsy. However, the duration of treatment has been relatively brief, particularly considering the chronic nature of the disease.

Methods: Sixty-nine patients with narcolepsy, who completed a 6-week crossover study of modafinil continued on modafinil for 16 weeks of open-label treatment (300 ± 100 mg). This was followed by 2 weeks during which patients were randomly and blindly allocated to continue modafinil (M) at the same dose ($n = 30$), or placebo (P; $n = 33$).

Results: A mean dose of 330 mg of modafinil continued to produce a significant decrease in EDS as measured by the Maintenance of Wakefulness Test (9.7 ± 7.9 for P; 16.4 ± 13.7 for M; $P = 0.009$), the Epworth Sleepiness Scale (15.4 ± 5.8 for P; 13.2 ± 5.7 for M; $P = 0.023$), and the number of episodes of severe somnolence and sleep reported in patient diaries (8.2 ± 7.2 for P; 4.2 ± 5.2 for M; $P = 0.017$). Modafinil had no significant effects on nocturnal sleep, blood pressure, heart rate, the electrocardiogram (ECG), weight, or mood.

Conclusion: Modafinil continues to be an effective and well-tolerated drug after 16 weeks of treatment.

Keywords: Modafinil; Narcolepsy; Controlled clinical trial; Therapeutic use; Administration and dosage; Drug effects; Adverse effects

1. Introduction

Controlled [1–5] and uncontrolled [6,7] trials have shown modafinil to be a safe and effective treatment for excessive daytime sleepiness (EDS) in patients with narcolepsy and with idiopathic hypersomnia. However, the duration of treatment over which modafinil has been evaluated is relatively brief, less than four weeks in most controlled studies and nine weeks in another [5]. Moreover, the possibilities of either drug tolerance or the appearance of delayed adverse effects of modafinil have not been assessed in long-term controlled trials. Narcoleptics in the current study were initially treated for 2 weeks with placebo, modafinil 200 mg, and modafinil 400 mg in a 6-week,

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three-period, randomized, double-blind, crossover trial [4]. Both doses of modafinil were safe and effective. In this paper we report on the long-term efficacy and safety of modafinil in those patients who were studied across a 16-week period in an open-label design, followed by a 2-week randomized double-blind period of either continuation of modafinil or placebo.

Our objective was to determine whether, at the end of the 2-week randomized double-blind period, there continued to be a significant difference in daytime somnolence between the two groups following 16 weeks of treatment with modafinil.

2. Methods

All patients met the International Classification of Sleep Disorders (ICSD) diagnostic criteria for narcolepsy [8] and had moderate or severe daytime sleepiness producing a moderate or marked impairment of social or occupational functions. Female patients of child bearing potential had a negative serum pregnancy test and were using an effective birth-control method. Patients agreed to refrain from operating a motor vehicle and from being involved in any other potentially hazardous activity during the double-blind phases of the study. All patients provided informed consent to a protocol that had received approval from the local Canadian research ethics boards.

Patients were excluded for any of the following reasons: amphetamine treatment in the last two months; excessive daytime sleepiness related to sleep apnea, periodic limb movement disorder, alcohol consumption; circadian rhythm disorder, insufficient sleep or other known syndromes leading to EDS; shift work; a history of head trauma; known hypersensitivity to modafinil; agitated states or severe anxiety; clinical depression; moderate or severe psychosis or dementia; dyskinesia; active peptic ulcers; hyperthyroidism; symptomatic cardiovascular disease; glaucoma; concurrent psychiatric, neurological, neoplastic, endocrinological, or infectious disease which may contribute to EDS; illicit drug use; the use of antipsychotic medication; or the use of any medication which might influence sleep (particularly REM (rapid eye movement) sleep) or contribute to EDS, except for anti-cataplectic medication which was continued in constant dosage. Narcoleptic patients with coexistent significant sleep apnea (apnea index >10 or a respiratory disturbance index >20) were also excluded from the trial.

Patients were assessed at baseline and at the end of each of three 2-week double-blind cross-over periods. These results have been previously described [4].

Following the 6-week double-blind crossover study, patients received modafinil under open-label conditions for 16 weeks, starting at a dosage of 200 mg in the morning and 100 mg at noon. During this period, patients adjusted their modafinil in 100 mg increments (or decrements) to the dose that best suited him or her with a maximum daily dosage of 500 mg. At the end of this period, patients were randomized in double-blind fashion to a 2-week treatment period with either their individualized dosage regimen of modafinil or an equivalent number of placebo tablets. We assessed efficacy and safety at the beginning and end of the 2-week period.

Placebo tablets were identical to the active tablets in all respects except for the absence of the active drug substance. All tablets were packaged in identical bottles, each labeled with a unique code, which was held in a locked cabinet at the sponsor's office. Patients were randomized at the beginning of the 16-week open period. Randomization (using Microsoft Excel's random number generator) was in balanced blocks of four and was stratified by center. Patients, study personnel, and the sponsor's monitor were all blinded.

The primary efficacy variables were the mean sleep onset latency on the Maintenance of Wakefulness Test (MWT) [9] and the mean number of sleep episodes and periods of severe sleepiness reported in a diary. The MWT consisted of four 40-minute nap opportunities separated by 2 h. Identical La-Z-Boy® model 505 recliners were provided to the centers for the MWT. The instructions to be given to the patients prior to lights out were standardized across centers. The diary was a log of patients' sleep–wake behavior, drug consumption, and cataplexy attacks, during the second of the 2 weeks. Also in the diary, patients rated the effect of EDS on a selected daily activity, using a 5-point ordinal scale (none-to-severe).

Sleepiness was also assessed using the Epworth Sleepiness Scale (ESS) [10]. Performance was assessed with the four-choice reaction time test

(FCRTT) [11]. Prior to overnight polysomnography (PSG) patients evaluated their mood during the previous week using the Profile of Mood States (POMS) [12]. On the day of the MWT, blood was drawn for hematology and biochemistry tests. Blood pressure and pulse were measured prior to the first dose, and then prior to each nap opportunity.

At the beginning and end of the 2-week period, patients were questioned regarding the appearance, worsening, or disappearance of any unusual signs or symptoms.

For overnight polysomnography, the MWT, the Epworth Sleepiness Scale, the Four-Choice Reaction Test, and the POMS, data from the end of the 2-week blinded period were compared between the modafinil and placebo groups by analysis of variance using data from the beginning of the 2-week blinded period as a covariate.

The number of periods of severe sleepiness, voluntary sleep episodes (naps), and sleep attacks were analyzed by analysis of variance. The quality of sleep and the effect of somnolence on a selected daily activity were analyzed by chi-square analysis.

Descriptive statistics of the data from the earlier cross-over period are provided as a reference. The study was not designed to compare data from the two blinded periods therefore no inferential analyses were done.

The sample size (see below) was chosen so that the initial cross-over study would be able to detect a 25% difference in mean sleep latency with a power of 80% at an α of 0.05.

3. Results

Of the 75 patients enrolled into the initial 6-week three-period cross-over study, four patients dropped out during that study period and two patients declined to continue on modafinil for the 16-week open period. Sixty-nine patients therefore enrolled into the open phase of the study; 63 patients completed the full 16 weeks of open treatment and were randomized to either continued modafinil ($n = 30$) or placebo ($n = 33$). Reasons for discontinuing were: lack of perceived therapeutic benefit (3); lost to follow-up (1); headaches, depression, and lethargy (1); seasonal mood disorder (1). Two additional patients, both randomized to modafinil, did not return for the final visit at the end of 2-week double-blind period due to concurrent illnesses (chest infection and flu). Both of them did, however, hand in the patient diary.

3.1. Demographic data

Patients were mostly middle-aged (45 ± SD of 16 years) Caucasian (92%) females (66.7%). They had had EDS for 24 ± 15 years. The diagnosis of narcolepsy had been made 17 ± 13 years after the onset of EDS. Fifty-eight of the 69 patients (84%) met the ICSD diagnostic criteria by virtue of having a history of cataplexy (although many no longer had attacks due to their anti-cataplectic medication). All patients met the polysomnographic and MSLT criteria. The mean pre-study diagnostic MSLT latency was 3.7 ± 2.6 min.

At baseline testing, half (50.8%) of patients were being treated with stimulant medication; the other half were untreated. Three quarters of the treated patients (24/32) were taking methylphenidate with a median daily dose of 30 mg (range 10–60 mg). Seven patients were taking pemoline (median 56.25 mg, range 37.5–75.0 mg). A single patient was being treated with mazindol, 1 mg per day. The mean duration of prior treatment was 4.6 (±7.5) years. Anti-cataplectic medications were continued at the same dose throughout the study. Twenty-four patients (38%) were being treated with one (or, in two cases, two) of eight different medications: amitriptyline (1), clomipramine (6), fluoxetine (5), imipramine (2), paroxetine (1), protriptyline (8), sertraline (1) and gamma-hydroxybutyrate (5).

3.2. Modafinil dosage

At the end of the 16-week open period, and during the 2-week double-blind phase, the mean (±SD) daily dose of modafinil was 329 ± 61 mg. Ninety-five percent (95%) of the patients remained within the range of 200 to 400 mg daily (one patient took 150 mg and two patients took 500 mg). The mean morning dose was 186 ± 44 mg, the mean mid-day dose was 144 ± 67 mg. Four patients (7%) had discontinued the mid-day dose and took a single morning dose of modafinil (three patients took a single morning dose of 200 mg and one took 400 mg). There was no evidence, either by reported doses or by tablet counts,

that daily consumption increased over the 16-week open period.

3.3. Efficacy

At the end of the 2-week blinded period (week 24), MWT mean sleep latencies were 70% longer on modafinil than on placebo ($P = 0.009$). In patients changed from modafinil to placebo, the mean sleep latencies decreased by 37% ($P = 0.006$), compared to a decrease of 7% in the group who remained on modafinil ($P = 0.35$). The latencies on modafinil were comparable to those from the cross-over period, 16 weeks earlier (Table 1).

Latency to the first epoch of stage 1 was also longer (6.4 ± 4.7 on P; 10.3 ± 8.6 on M; $P = 0.035$). A greater number of MWT test sessions ended without sleep on modafinil (6.1% on P; 24.3% on M; $P < 0.001$). This difference was consistent across all four sessions. Modafinil increased mean sleep latencies at each of the four individual sessions (Fig. 1).

Compared to placebo, modafinil reduced the total number of reported episodes of severe somnolence plus sleep attacks plus naps ($P = 0.017$). The magnitude of the difference was greater than that seen during the earlier cross-over period (Table 2).

Table 1
MWT sleep latencies[a]

	Placebo	*n*	Modafinil	*n*
On placebo during x-over (week 2, 4, or 6)	10.7 ± 8.9	33	11.7 ± 11.4	30
200 mg modafinil during x-over (week 2, 4, or 6)	15.8 ± 12.1	33	16.9 ± 13.7	30
400 mg modafinil during x-over (week 2, 4, or 6)	18.1 ± 12.7	33	17.9 ± 13.6	30
On modafinil at end of open-label (week 22)	15.3 ± 12.2	33	17.7 ± 14.0	30
End of parallel double-blind (week 24)	9.7 ± 7.9	33	16.4 ± 13.7	28

[a] Mean ± SD sleep latencies on the 40-min maintenance of wakefulness test.

The effect of sleepiness on a chosen activity was

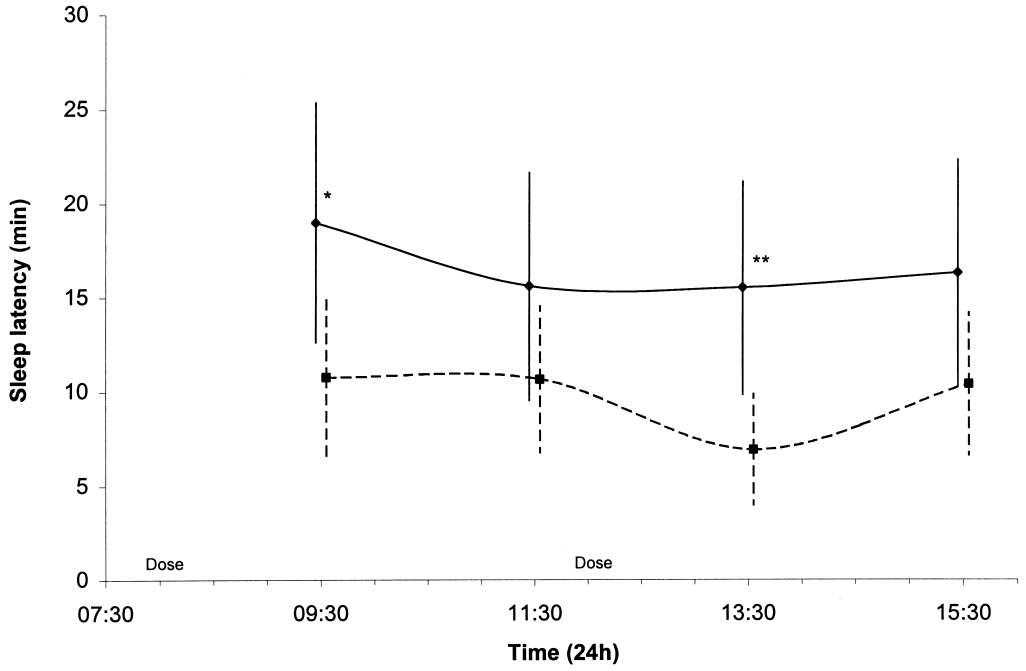

Fig. 1. Mean sleep latency (± 95% confidence interval) on the maintenance of wakefulness test (— modafinil; - - - placebo). * $P < 0.05$, ** $P < 0.01$.

Table 2
Periods of severe somnolence + sleep attacks + naps[a]

	Placebo	*n*	Modafinil	*n*
On placebo during x-over (week 2, 4, or 6)	6.5 ± 6.2	30	6.3 ± 6.0	29
200 mg modafinil during x-over (week 2, 4, or 6)	5.4 ± 5.7	31	4.5 ± 4.3	29
400 mg modafinil during x-over (week 2, 4, or 6)	5.3 ± 5.0	31	5.0 ± 5.7	29
End of parallel double-blind (week 24)	8.2 ± 7.2	18	4.2 ± 5.2	30

[a] Mean ± SD daily number of episodes of severe somnolence + naps + sleep attacks, recorded in the patient diary on the second week of each 2-week period.

not different. The chosen activities included: reading ($n = 16$); intellectual activities other than reading such as computer work, schoolwork, accounting, playing guitar, etc. ($n = 16$); physical activities including housework, cooking, and farm work ($n = 12$); watching TV ($n = 11$); being in a car ($n = 4$); and other ($n = 3$). Only in the subset of intellectual activities, was a significant drug effect detected. Fifty percent of the ratings by patients on placebo evaluated the effect of EDS on the selected (intellectual) daily activity as marked or severe, compared to 25% of ratings by patients on modafinil ($P = 0.02$). The mean daily number of cataplectic attacks was low and not different between treatments (0.11 ± 0.27 for M; 0.19 ± 0.59 for M; $P = 0.48$).

Consistent with diary results, ESS scores at week 24 were lower on modafinil compared to placebo ($P = 0.023$). The likelihood of falling asleep increased by 19% when patients discontinued modafinil ($P = 0.007$) and remained unchanged in the modafinil group (+ 1%; $P = 0.57$) (Table 3).

On the FCRT, no differences were detected in reaction time, number of gaps, or number of errors.

3.4. Tolerance and safety

There was no difference between placebo and modafinil groups on either the total mood disturbance score or on any of the POMS factors. No adverse effects on mood were detected after abruptly discontinuing modafinil. Also, the total mood disturbance score was unchanged after 16 weeks of modafinil (compared to the placebo period in the crossover study).

Modafinil had no chronic effect on blood pressure or heart rate. Patients switched from modafinil to placebo had no change in vital signs. Sixteen weeks of modafinil did not change morning pre-dose blood pressure or heart rate (Table 4).

Acute post-dose effects were seen on standing (but not supine) diastolic blood pressure at 13 h 30 (mean + 2.7 Torr; 95% CI, 0.3–5.2); and supine, but not standing, HR was higher at 11 h 30 (95% CI, 0.5–4.9 bpm), 13 h 30 (95% CI, 1.3–6.1 bpm), and 15 h 30 (95% CI, 1.3–6.1). Compared to baseline, the twelve-lead ECG was unchanged after the open-label period, and at the completion of the study.

Modafinil had few effects on measures of sleep initiation, sleep maintenance and sleep architecture compared to placebo. The only significant effects were a shortened latency to stage 4 sleep (54.8 ± 57.2 on P; 36.3 ± 28.1 on M; $P = 0.05$) and an increase in % stage 4 sleep (8.9 ± 11.3 on P; 10.8 ± 7.8 on M; $P = 0.02$). Total sleep time on modafinil was 406.1 ± 68.9 min compared to 403.1 ± 66.8 min on placebo. Consistent with the PSG findings, modafinil had neither a detrimental nor a beneficial effect

Table 3
Epworth Sleepiness Scale[a]

	Placebo	*n*	Modafinil	*n*
On placebo during x-over (week 2, 4, or 6)	16.3 ± 4.4	33	16.6 ± 4.8	30
200 mg modafinil during x-over (week 2, 4, or 6)	14.2 ± 5.9	31	15.8 ± 5.8	30
400 mg modafinil during x-over (week 2, 4, or 6)	14.0 ± 6.2	31	14.2 ± 5.2	29
On modafinil at end of open-label (week 22)	12.9 ± 6.7	33	13.4 ± 6.0	30
End of parallel double-blind (week 24)	15.4 ± 5.8	33	13.2 ± 5.7	28

[a] Mean ± SD total Epworth Sleepiness Scale score for the second week of each 2-week period.

Table 4
Blood pressure and heart rate[a]

	Placebo		Modafinil	
	SBP/DBP	HR	SBP/DBP	HR
On placebo during x-over (week 2, 4, or 6)	123/73	68	119/72	66
200 mg modafinil during x-over (week 2, 4, or 6)	120/72	68	119/71	66
400 mg modafinil during x-over (week 2, 4, or 6)	122/72	68	122/74	69
On modafinil at end of open-label (week 22)	123/72	69	119/72	70
End of parallel double-blind (week 24)	124/73	70	118/73	69

[a] Mean morning pre-dose supine blood pressure and heart rate.

on either the quantity or the subjective quality of nocturnal sleep as reported in the diaries (Table 5).

On modafinil, 49% rated their sleep as 'good' compared to 42% on placebo; and 20% reported sleep as 'poor', compared to 22% on placebo.

Weight changes during the open-label period were insignificant (mean + 0.13 kg; 95% CI, 0.59–0.85). Thirty patients lost weight, 24 gained weight, weight was unchanged in three (Table 6).

During the 2 weeks of blinded treatment, the incidence of adverse effects on modafinil was not different from that on placebo. Headache was reported most frequently with three patients in each group. Three patients complained of abdominal pain; all were on placebo. Two patients, both on modafinil, complained of nervousness. No other adverse effects were reported by more than one patient.

During the 16-week open period, there were 113 complaints involving 42 different adverse events reported by 43 patients. The most frequent complaints were headache (13%), dry mouth (11.6%) and nervousness (7.2%).

No hematological changes were seen over the nearly 6 months of treatment. Mean transaminase values remained within the upper limit of normal and did not change significantly. The 95% confidence intervals for the changes from baseline were −0.4–3.6 units for AST; and −0.3–5.2 units for ALT. AST increased in 32 patients and decreased in 25 patients. ALT increased in 36 patients and decreased in 20. Only two patients had concomitant increases in both AST and ALT. In neither of these patients did alkaline phosphatase change significantly. No significant changes in alkaline phosphatase were seen either overall or in individual patients (95% CI, −4.0–2.4).

4. Discussion

After nearly 6 months of treatment, modafinil continued to have a significant effect on improving EDS as measured by the MWT, the Epworth Sleepiness Scale and a patient diary, as well on activities of an intellectual nature. Over the course of our study there was no decrease in the strength of the response and patients did not increase their dose. The magnitude of the difference on the MWT between placebo and an average daily dose of 330 mg of modafinil (an increase of 70%), was greater than that found in these same patients in the cross-over study (45% on 200 mg; 61% on 400 mg). This is consistent with the absence

Table 5
Nocturnal sleep[a]

	Placebo		Modafinil	
	Diary	PSG	Diary	PSG
On placebo during x-over (week 2, 4, or 6)	7.4 ± 1.1	6.6 ± 1.0	7.1 ± 1.1	6.6 ± 1.3
200 mg modafinil during x-over (week 2, 4, or 6)	7.5 ± 1.1	6.4 ± 1.3	6.9 ± 1.1	6.6 ± 1.0
400 mg modafinil during x-over (week 2, 4, or 6)	7.2 ± 1.1	6.3 ± 1.3	7.2 ± 1.3	6.6 ± 1.2
On modafinil at end of open-label (week 22)	n/a	6.5 ± 1.2	n/a	6.6 ± 1.1
End of parallel double-blind (week 24)	7.1 ± 1.1	6.7 ± 1.1	7.0 ± 1.3	6.6 ± 1.1

[a] Nocturnal sleep (h): subjective evaluation from patient diary and TST from nocturnal PS.

Table 6
Weight (kg)

	Placebo	*n*	Modafinil	*n*
On placebo during x-over (week 2, 4, or 6)	78.9 ± 16.8	33	81.2 ± 18.7	28
200 mg modafinil during x-over (week 2, 4, or 6)	76.9 ± 16.3	29	81.2 ± 18.9	28
400 mg modafinil during x-over (week 2, 4, or 6)	77.3 ± 16.1	31	79.7 ± 18.6	28
On modafinil at end of open-label (week 22)	77.5 ± 17.5	30	81.6 ± 18.6	29
End of parallel double-blind (week 24)	79.0 ± 18.5	29	81.5 ± 18.4	27

of the development of any tolerance. These results are also consistent with the early report of Bastugi and Jouvet [6] who found no evidence of loss of effectiveness during their 2-month open-label study. A few of their patients were followed for 2–3 years without any evidence of tolerance or dependence.

Few long duration studies of the compound's effectiveness on objective laboratory measures of sleepiness exist. In order to compare our results with other studies, we re-analyzed the MWT data using a 20 minute cut-off. Sleep latencies on modafinil (10.8 ± 6.8) were 38% longer than on placebo (7.8 ± 4.5). The difference is comparable to the 34% reported by Besset et al. [1] in patients taking placebo or modafinil 300 mg daily for 4 weeks (8.2 on placebo, 11.0 on modafinil). The absolute difference between modafinil and placebo is comparable to that reported by the US Modafinil in Narcolepsy Multicenter Study Group [5] after nine weeks of treatment with either placebo (5.8 ± 4.7), modafinil 200 mg (8.1 ± 6.1), or modafinil 400 mg (8.9 ± 6.2). The sleep latencies in their groups were lower than ours, possibly due to the fact that all of their patients had cataplexy while 16% of our patients did not. The EDS was less severe in our patients without cataplexy, although their response to modafinil was not different.

Modafinil was well tolerated. In contrast to the prototypical psychostimulants, modafinil had no effect on mood, weight, blood pressure and heart rate. Modafinil did not affect the quality of night sleep, a finding present in PSG recordings in all reported trials [1–5]. No patient on antidepressants required a dosage adjustment and cataplexy remained unchanged, suggesting the absence of any significant drug interactions.

Headache, which was the principle adverse effect, did not occur more frequently than with placebo. During the preceding 6-week crossover period, dizziness and nausea, headaches, nervousness, and dry mouth were the most frequently reported adverse events. The data suggests that many of the initial symptoms were not troublesome with continued treatment.

In conclusion, this study shows that modafinil continues to be an effective and well-tolerated drug after 16 weeks treatment of excessive daytime sleepiness in patients with narcolepsy.

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