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Dosing Regimen Effects of Modafinil for Improving Daytime Wakefulness in Patients With Narcolepsy

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Summary: In a multicenter, randomized, double-blind study the authors compared the efficacy of modafinil 400 mg once daily, 400 mg given in a split dose, or 200 mg once daily for maintaining wakefulness throughout the day in patients (N = 32) with narcolepsy reporting a positive daytime response to modafinil but late-afternoon/evening sleepiness. Efficacy evaluations included an extended Maintenance of Wakefulness Test (9:00 AM to 9:00 PM), the Clinical Global Impression of Change scale, and the Epworth Sleepiness Scale. Modafinil demonstrated significant improvement in wakefulness as assessed by the Epworth Sleepiness Scale compared with placebo at baseline (all $P < 0.001$). Modafinil significantly improved patients' ability to sustain wakefulness, as demonstrated by mean sleep latency at week 3 compared with placebo at baseline (all $P < 0.001$). The 400-mg split-dose regimen improved wakefulness significantly in the evening compared with the 200-mg and 400-mg once-daily regimen (both $P < 0.05$). The percentage of patients rated as "much improved" or "very much improved" with respect to evening sleepiness was 27%, 82%, and 80% in the 200-mg, 400-mg once-daily, and 400-mg split-dose groups, respectively. Adverse events were mild to moderate in nature and included headache, nausea, nervousness, dyspepsia, pain, and vomiting (all 6%). Some patients may benefit from 400-mg doses of modafinil taken once daily compared with 200-mg doses. A split-dose 400-mg regimen may be superior to once-daily dosing for sustaining wakefulness throughout the entire waking day. **Key Words:** narcolepsy, sleepiness, wakefulness, modafinil, dose

Modafinil, a novel wake-promoting agent, is an effective and well-tolerated treatment for improving wakefulness in patients with excessive sleepiness associated with narcolepsy.[1–3] Although the specific mechanism of action of modafinil is unknown, modafinil appears to promote wakefulness by selectively affecting discrete areas of the brain, such as the anterior hypothalamus, responsible for maintaining normal wakefulness.[4] Subsequently, modafinil may activate the cortex via excitatory pathways that are histaminergic and perhaps orexogenic.[4] This increase in wakefulness has been associated with a significant increase in the excitatory amino acid glutamate ($P < 0.05$)[5] and with a significant decrease in the inhibitory neurotransmitter γ-aminobutyric acid ($P < 0.05$).[6] Modafinil has been shown to be ineffective in a preclinical study of dopamine transporter knockout mice,[7] suggesting that an intact dopamine system may be necessary for its effect. Modafinil is only a weak inhibitor of the dopamine transporter site and, unlike stimulants, modafinil-induced wakefulness is not antagonized by haloperidol.[6,8] Modafinil is not a direct or indirect dopamine agonist.[8,9] Furthermore, the chemical and pharmacologic profile of modafinil is different from that of amphetamine and methylphenidate.[10–12] Although an intact dopamine system may be necessary for modafinil

Drs. Schwartz, Feldman, and Bogan were investigators involved with the clinical trial whose results are being reported in this manuscript. Dr. Schwartz also functions as a consultant to Cephalon, Inc. Dr. Feldman is part of the Cephalon speakers bureau. Mr. Nelson and Dr. Hughes are Cephalon employees. In addition, this manuscript does not contain information regarding off-label or the investigational use of modafinil.

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to have its effect,[7] in various preclinical and clinical studies, modafinil has been found to have substantially lower abuse potential.[13–18]

Modafinil has been recommended by the American Academy of Sleep Medicine as a "standard" therapy for improving wakefulness in patients with narcolepsy,[19] with a proven safety profile during short- and long-term treatment.[20,21] In 2 9-week, large-scale, double-blind, placebo-controlled, clinical trials,[2,3] both 200-mg and 400-mg once-daily doses of modafinil significantly facilitated wakefulness compared with placebo treatment on objective and subjective measures of sleepiness (all $P < 0.05$). In other studies, split-dose regimens of modafinil were shown to significantly promote wakefulness[1,21,22] without adversely affecting nighttime sleep.[1,21] To our knowledge, ours is the first study to compare directly once-daily versus split dosing for promoting wakefulness in patients with excessive sleepiness associated with narcolepsy. The objective of the current study was to compare the efficacy of a modafinil 400-mg once-daily regimen and a modafinil 400-mg split-dose regimen with that of modafinil 200 mg once daily for maintaining wakefulness throughout the entire waking day.

MATERIALS AND METHODS

Study Design and Dosing

This study, which was conducted at 3 centers, had a 3-week study, 3-period, randomized, double-blind, crossover design. The institutional review board at each center approved the protocol, and all patients gave written informed consent. Patients were randomized to 1 of 3 treatment sequences using a 3 × 3 Latin square design. The titration and dosing schedule for each regimen administered during the treatment sequences is shown in Figure 1.

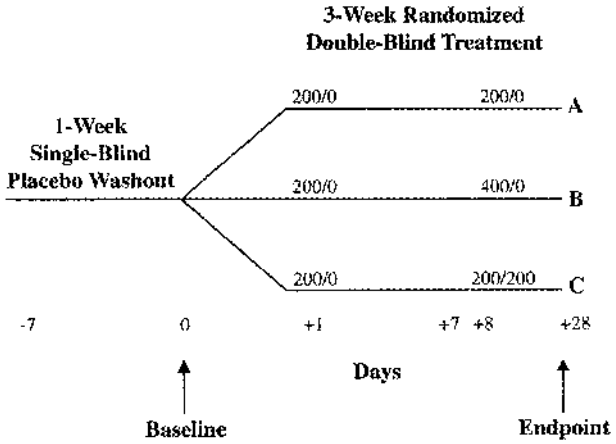

Figure 1. Study design. Each treatment was preceded by a 1-week, single-blind placebo washout period during which patients received matching placebo in the morning (4 tablets) and at noon (2 tablets). The treatment period was double-blinded for 3 weeks. The dosing schedule for the first week for all treatment groups was as follows: 200 mg modafinil (2 tablets) plus 2 placebo tablets at 7:00 AM, 2 placebo tablets at 12:00 noon. The dosing schedules for the remaining 14 days for the 3 treatment groups were as follows: A = 200 mg once daily, 200 mg modafinil (2 tablets) plus 2 placebo tablets at 7:00 AM, 2 placebo tablets at 12:00 noon; B = 400 mg once daily, 400 mg modafinil (4 tablets) at 7:00 AM, 2 placebo tablets at 12:00 noon; C = 400 mg split dose, 200 mg modafinil (2 tablets) plus 2 placebo tablets at 7:00 AM, 200 mg modafinil (2 tablets) plus 2 placebo tablets at 12:00 noon. For the two 400-mg/day treatment regimens, an upward titration to the final dose was used over the first 14 days of treatment.

Patients

Adult patients with a current diagnosis of narcolepsy, as defined by the American Sleep Disorders Association,[23] nocturnal polysomnography, Multiple Sleep Latency Test performed within 5 years of the screening visit, and a positive therapeutic response to modafinil but dissatisfaction with late-afternoon or evening sleepiness, and a Clinical Global Impression (CGI) of severity[24] rating of greater than or equal to 4 points (moderately ill or worse) with respect to late-afternoon/evening sleepiness at the screening visit were included. Patients were excluded if they had a habitual wake-up time after 8:00 AM, active clinically significant medical disorders other than narcolepsy, disorders other than narcolepsy considered to be the primary cause of excessive sleepiness, apnea/hypopnea (>10 events per hour of sleep), a mean Maintenance of Wakefulness Test (MWT) time for the first 4 sessions at placebo baseline of less than 12 minutes, a history of drug abuse, consumed excessive amounts of caffeine-containing beverages or foods (≥500 mg/day caffeine), or had a requirement for certain medications (eg, tricyclic antidepressants, methylphenidate, amphetamines, pemoline, barbiturates, antipsychotic agents, monoamine oxidase inhibitors, anticoagulants, benzodiazepines, and anticonvulsants).

Assessments

Patients visited the clinic at placebo baseline for each treatment period (ie, after completing a 1-week washout period) and again at the end of each 3-week treatment period. Efficacy was assessed using a modified version of the MWT,[25] the CGI of Change,[24] and the Epworth Sleepiness Scale (ESS).[26] The modified MWT included sessions conducted at placebo baseline and at the end of each treatment regimen in the morning (9:00 AM and 11:00 AM), afternoon (1:00 PM and 3:00 PM), and evening (5:00 PM and 7:00 PM). Thirty-minute MWT sessions were used to minimize the potential for a ceiling effect in some patients on active treatment.[27] Patients were instructed to eat breakfast at 7:00 AM,

lunch as close as possible to noon, and dinner at approximately 6:00 PM. A snack was offered to each patient at approximately 4:00 PM. The time to sleep onset was scored based on standard Rechtschaffen and Kales[28] criteria (defined as 3 consecutive epochs of stage 1 sleep or 1 epoch of any other sleep stage). Data from the final session (9:00 PM) of the MWT were not included a priori in any analysis because of the potential for a "last session" effect resulting from patients' anticipation of going home.[29] The CGI of Change, the ESS, a brief physical examination, and vital sign measurements were conducted after the 3:00 PM session. Adverse events were recorded throughout the study, and standard clinical laboratory tests were performed. A complete physical examination and an electrocardiogram were performed at the screening and final visit.

Statistical Analysis

An analysis of variance model including terms for treatment, period, study site, patient, and treatment-by-period interaction indicated a significant treatment-by-period interaction for MWT sleep latency times across the 3 periods ($P = 0.007$). Therefore, all efficacy variables were evaluated for treatment period 1 only, resulting in a double-blind, parallel-group design. An analysis of covariance model using rank-transformed data,[30] with treatment as a factor and placebo baseline value as a covariate, was performed for comparisons between treatment groups for each continuous variable (ie, the mean change from placebo baseline in the MWT sleep latency time for the 6 sessions from 9:00 AM to 7:00 PM; the mean change from placebo baseline in the morning, afternoon, and evening sessions of the MWT; and the mean change from placebo baseline in the ESS total score). Intragroup comparisons between placebo baseline and end point values were made using a paired *t*-test on rank-transformed data. Intergroup comparisons were performed using logistic regression analysis with treatment as a factor and placebo baseline value as a covariate. CGI of Change results were analyzed using a proportional odds model, with treatment as a factor and placebo baseline value as a covariate. All statistical tests were 2 sided and were performed at the 5% level of significance. All patients who received the study drug were included in the safety analysis.

RESULTS

Patients

Demographic and placebo baseline information of the 32 patients randomized to treatment are presented in Table 1.

TABLE 1. *Characteristics of randomized patients according to dosing regimen in period 1*

Characteristic	Modafinil 200 mg QD (n = 11)	Modafinil 400 mg QD (n = 11)	Modafinil 400 mg SD (n = 10)
Age, y			
Mean (stand. dev.)	43 (12)	47 (16)	39 (15)
Range	28–61	28–71	19–60
Gender, n (%)			
Male	3 (27)	7 (64)	5 (50)
Female	8 (73)	4 (36)	5 (50)
Sleep latency, min (MWT)*			
Mean (stand. dev.)	10.5 (10.21)	16.8 (11.12)	9.9 (8.36)
Excessive sleepiness total score (ESS)			
Mean (stand. dev.)	17.3 (3.17)	15.6 (1.80)	15.3 (2.67)
Disease severity (CGI-S)†, n (%)			
Moderately ill	5 (45)	4 (36)	4 (40)
Markedly ill	4 (36)	7 (64)	5 (50)
Severely ill	1 (9)	0	0
Among the most extremely ill	1 (9)	0	1 (10)
Modafinil dose at screening, mg			
Mean (stand. dev.)	345 (82)	378 (67)	333 (100)
Range	200–400	200–400	200–400

MWT, Maintenance of Wakefulness Test; ESS, Epworth Sleepiness Scale; CGI-S, Clinical Global Impression of Severity; QD, once-daily dose (morning); SD, split dose (morning and noon); stand. dev., standard deviation.

* For the sixth session.

† Patients enrolled were required to have a rating of moderately ill or worse with respect to late-afternoon/evening sleepiness.

Efficacy Assessments

Maintenance of wakefulness test

All 3 modafinil dosing regimens significantly improved patients' ability to sustain wakefulness, as shown by improvement in the mean MWT sleep latency (all $P < 0.001$; Fig. 2). The improvements from placebo baseline in mean MWT sleep latency times for both modafinil 400-mg dosing regimens were significantly longer than the mean time for the 200-mg once-daily regimen (both $P < 0.05$). No significant difference was observed between the mean change from placebo baseline in sleep latency time for the 400-mg once-daily and the 400-mg split-dose regimens.

As shown in Figure 3, the mean change from placebo baseline in the MWT sleep latency time in the evening indicated a significantly greater improvement in wakefulness for patients receiving the modafinil 400-mg split-dose regimen than for those receiving 200 mg once daily ($P < 0.001$) and for those receiving 400 mg once daily ($P < 0.05$).

The percentage of patients able to sustain wakefulness was highest in the morning for patients in the modafinil 400-mg once-daily group and highest in the evening for those in the modafinil 400-mg split-dose group. In the evening, a significantly higher percentage of patients receiving the modafinil 400-mg split-dose regimen remained awake for the first 20 minutes compared with those receiving modafinil 200 mg once daily or 400 mg once daily (all $P < 0.05$; Fig. 4).

Clinical global impression of change

All 3 modafinil dosing regimens improved the overall clinical condition compared with placebo baseline. With respect to evening sleepiness, the percentage of patients rated as "much improved" or "very much improved" was 27% for the modafinil 200-mg once-daily group, 82% for the modafinil 400-mg once-daily group, and 80% for the modafinil 400-mg split-dose group. The percentage of patients rated as at least "improved" was 91% for those taking modafinil 400 mg once daily and 90% for patients receiving the modafinil 400-mg split-dose regimen, with both 400-mg treatment groups demonstrating a significantly greater improvement in evening sleepiness than the 200-mg once-daily group (54%, both $P < 0.05$).

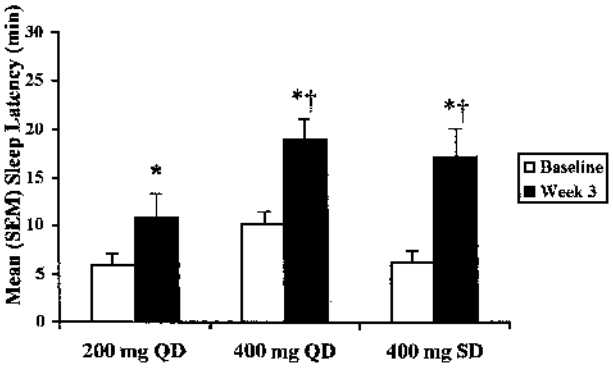

Figure 2. Mean (standard error of the mean) sleep latency times at placebo baseline and after 3 weeks of treatment of the first 6 sessions of the Maintenance of Wakefulness Test (9:00 AM–7:00 PM) according to the dosage of modafinil in period 1. *$P < 0.001$ for the intragroup comparison with placebo baseline. †$P < 0.05$ for both 400-mg doses compared with the 200-mg dose. QD, once daily; SD, split dose.

Epworth sleepiness scale

Mean ESS scores indicated significantly improved wakefulness in patients treated with all 3 dosages of modafinil compared with mean scores at placebo baseline ($P < 0.001$ for the intragroup change from placebo baseline). The mean change from placebo baseline in the ESS score for patients treated with the modafinil 400-mg once-daily regimen demonstrated a trend for a greater improvement in wakefulness than that observed for patients receiving the 200-mg once-daily regimen, although this effect did not achieve statistical significance.

Safety Assessments

No marked differences were observed in the frequency or severity of adverse events among the different treatment groups. The most commonly occurring adverse events (all mild to moderate in nature) reported during the entire study were headache, nausea, nervousness, dyspepsia, pain, and vomiting (all 6%). Five patients reported adverse events (200 mg, n = 1; 400 mg once daily, n = 4). The results of laboratory tests, physical examinations, vital sign measurements, and electrocardiographic recordings indicated no clinically important treatment-related abnormalities.

One patient receiving 400 mg once daily (during the second treatment period) experienced adverse events (mild-to-moderate agitation, irritability, nervousness, anxiety, gastrointestinal distress, and insomnia) that led to temporary discontinuation of study medication. This was the only patient to report insomnia during the entire study.

DISCUSSION

The current investigation is the first to compare once-daily versus split-dosing regimens of modafinil throughout the entire waking day. The results of the extended MWT testing demonstrated for the first time that 400 mg, taken either once daily or as a split dose, was significantly better for facilitating wakefulness throughout the entire waking day (both $P < 0.05$) than

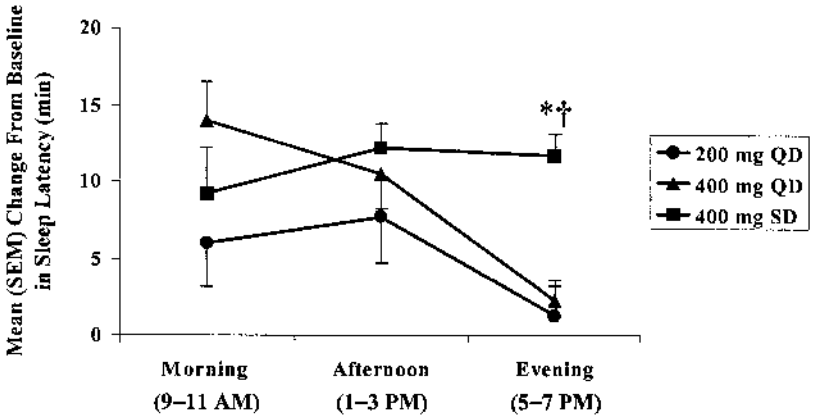

Figure 3. Mean (standard error of the mean) change from placebo baseline in Maintenance of Wakefulness Test sleep latency times for the morning (9:00 AM and 11:00 AM), afternoon (1:00 PM and 3:00 PM), and evening (5:00 PM and 7:00 PM) sessions according to the dosage of modafinil in period 1. *$P < 0.001$ for the intergroup comparison with 200 mg QD. †$P < 0.05$ for the intergroup comparison with 400 mg QD. QD, once daily (morning); SD, split dose (morning and noon).

200 mg once daily in this population. This finding was supported both by the objective measure of wakefulness (MWT sleep latency) and improvements in clinical condition (CGI) with respect to evening sleepiness. As reported previously in split-dose regimens of modafinil,[1,21] there were no effects on nighttime sleep in any of the treatment groups.

The finding that both 400-mg regimens of modafinil were significantly more effective than the 200-mg once-daily regimen for facilitating wakefulness throughout the day (both $P < 0.05$) is in contrast to that of 2 large-scale clinical trials that found no statistical difference in efficacy between 200-mg and 400-mg modafinil daily doses.[2,3] The modifications to the execution and timing of the MWT may have contributed to these differences. In the 2 pivotal trials, modafinil was administered approximately 1 hour before the first MWT. Because modafinil levels peak 2 to 4 hours after administration, the current study offered a greater opportunity to discriminate between the effects of 2 once-daily doses. Alternatively, the finding that 400 mg was superior to 200 mg may have been the result of subject selection. For instance, the current investigation included patients who were stabilized on higher doses (approximately 350 mg/day) of modafinil before the study initiation.

Late-afternoon/evening sleepiness has not been investigated clinically in many patients with narcolepsy,[31] largely because the accepted MWT protocol stipulates that testing be performed during 4 or 5 sessions at regular 2-hour intervals between early morning and mid afternoon.[32] In practice, some patients with narcolepsy are known to experience late-afternoon or evening sleepiness despite good treatment responses earlier in the day with modafinil. The current findings indicate that adding a second 200-mg dose of modafinil at midday is well tolerated and effective in sustaining wakefulness throughout the entire day in such patients.

Although these results may have important implications for the way in which modafinil may be optimally dosed, the study also has several limitations that should be considered. The current study, which had a randomized, double-blind, crossover design, reverted to a parallel-group design because of a significant treatment-by-period interaction. Nevertheless, significant improvements from placebo baseline were observed in objective and subjective measures of wakefulness and overall clinical condition for all 3 dosages of modafinil despite the small sample size for each treatment group (all $P < 0.05$). We included only patients with narcolepsy who had had a previous clinical response to modafinil. Because a patient's response to modafinil is

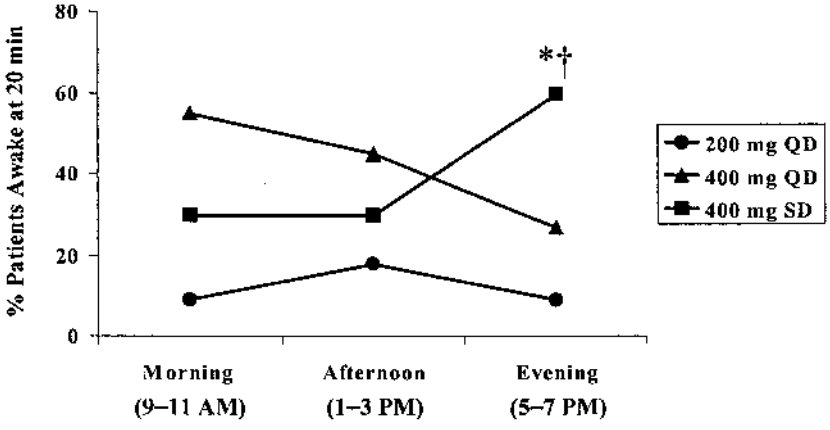

Figure 4. Proportion of patients remaining awake for the first 20 minutes of both Maintenance of Wakefulness Test sessions of the morning, afternoon, and evening according to the modafinil dosage in period 1. *$P < 0.05$ for the intergroup comparison with 200 mg QD. †$P < 0.05$ for the intergroup comparison with 400 mg QD. QD, once daily (morning); SD, split dose (morning and noon).

complex, involving genetic, immunologic, and environmental factors,[33] the observed magnitude of the clinical effects may be exaggerated with respect to the total narcolepsy population.

In addition, because patients were selected for evening sleepiness despite satisfactory daytime treatment, the observed time-of-day effects may not generalize to all patients with narcolepsy. This study, however, was designed to determine the relative advantage of various dose and dosing strategies for sustaining the wake-promoting effects of modafinil in this specific group of patients. Lastly, the current study did not include nocturnal polysomnographic recording to assess the potential effects of modafinil on sleep. However, several studies have demonstrated the lack of effects of 200-mg and 400-mg once-daily doses,[2,3] and 200-mg and 400-mg split doses[1] of modafinil on objectively recorded sleep.

In conclusion, the results of the current study suggest that some patients with narcolepsy who experience late-afternoon or evening sleepiness may benefit from 400-mg doses of modafinil, taken either once daily or as a split dose. Although all doses significantly improve wakefulness during traditional daytime working hours, the 400-mg split-dose regimen significantly improves wakefulness during the evening hours compared with once-daily dosing regimens.

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