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Original article

Efficacy and safety of modafinil for improving daytime wakefulness in patients treated previously with psychostimulants

Jonathan R.L. Schwartz[a,*], Neil T. Feldman[b], June M. Fry[c], John Harsh[d]

[a]*Integris Sleep Disorders Center of Oklahoma, Integris Southwest and Baptist Medical Centers, 4200 S. Douglas, Suite 313, Oklahoma City, OK 73109, USA*
[b]*St. Petersburg Sleep Disorders Center, St. Petersburg, FL, USA*
[c]*Center for Sleep Medicine, Philadelphia, PA, USA*
[d]*University of Southern Mississippi, Hattiesburg, MS, USA*

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Abstract

Objectives: To assess the efficacy and safety of modafinil for improving wakefulness in narcolepsy patients treated previously with psychostimulants.

Background: Modafinil has become a standard therapy for improving daytime wakefulness in narcolepsy patients and may be a useful therapeutic alternative to psychostimulants used to improve waking function in other medical conditions. Modafinil is chemically dissimilar to and has a pharmacological profile that differs from the psychostimulants. Modafinil has a low abuse potential and is well tolerated.

Methods: Patients ($N = 151$) with narcolepsy who had been unsatisfactorily treated with dextroamphetamine ($N = 48$), methylphenidate ($N = 66$), or pemoline ($N = 37$) were enrolled in this 6-week, open-label, multicenter study. Following a 2-week washout period, patients received modafinil once daily (Week 1, 200 mg; Weeks 2–6, 200 or 400 mg). Efficacy was evaluated at Weeks 1, 2, and 6 using the Epworth Sleepiness Scale and the Clinical Global Impression of Change. Adverse events were monitored throughout the study.

Results: Treatment with modafinil improved daytime wakefulness versus baseline regardless of which psychostimulant was taken previously. Mean ESS scores were improved after 1 week of treatment with modafinil. Improvements were maintained throughout the 6 weeks of treatment (all $P < 0.001$ versus baseline after washout). At Week 6, 79% of all patients were considered to be clinically improved relative to post-washout baseline. The most frequent adverse events were headache, nausea, and insomnia; the majority of adverse events were mild or moderate in nature. Approximately 70% of patients were receiving 400 mg of modafinil once daily at the end of the study.

Conclusion: During this 6-week, open-label study, modafinil was an effective and well-tolerated treatment for improving daytime wakefulness in narcolepsy patients previously treated with psychostimulants.

Keywords: Modafinil; Excessive daytime sleepiness; Wakefulness; Dextroamphetamine; Methylphenidate; Pemoline

1. Introduction

Pharmacotherapies for the treatment of sleepiness associated with narcolepsy and some other medical conditions have traditionally included the central nervous system (CNS) psychostimulants (e.g. amphetamines, methylphenidate). These agents enhance the neuronal release of biogenic amines, including dopamine, and block their reuptake [1]. The resulting generalized CNS stimulation results in improvements in alertness [2]. Because of their broad actions, however, the psychostimulants are associated with side effects and safety concerns that may limit their use in some patients. Side effects associated with the psychostimulants include central, cardiovascular, gastrointestinal, anorectic, and hepatic effects [3]. Rebound hypersomnolence may occur on treatment withdrawal [4]. The potential for development of tolerance with continued use of psychostimulants is widely recognized and presents clinical challenges for administering these agents [2]. In addition, amphetamines and methylphenidate have a higher potential for abuse.

Modafinil is a novel wake-promoting agent that is chemically dissimilar to and has a pharmacological profile that differs from the psychostimulants. Modafinil does not induce widespread activation of the CNS [5,6]. Rather, modafinil appears to promote cortical activation and arousal through the selective modulation of the central pathways implicated in the physiologic regulation of wakefulness [5,7]. Modafinil has been shown to activate wake-generating

* Corresponding author. Tel.: +1-405-636-1111; fax: +1-405-636-7995.
E-mail address: schwjr@integris-health.com (J.R.L. Schwartz).

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neurons in the tuberomammillary nucleus of the hypothalamus, which increase cortical activity via ascending histaminergic projections to the cortex [7].

In clinical trials, modafinil has been shown to improve wakefulness in patients with excessive sleepiness associated with a variety of sleep disorders including narcolepsy [8–15] and obstructive sleep apnea/hypopnea syndrome [16–19]. Moreover, modafinil was associated with significant improvements in overall health-related quality of life, including patients' emotional and psychological well being [20]. Efficacy has been maintained in open-label studies for up to 136 weeks [15,21,22].

Modafinil is considered a standard therapy for excessive sleepiness when narcolepsy patients are newly diagnosed or naïve to treatment and may be an effective alternative therapy when patients or physicians express dissatisfaction with prior psychostimulant therapy [23,24]. However, there are reports that modafinil may have reduced efficacy in some patients treated previously with high dose amphetamines or methylphenidate [10,25]. While it has been suggested that treatment naïve patients accept modafinil best [25], a retrospective analysis of data from 558 patients with narcolepsy demonstrated that modafinil was equally effective in promoting wakefulness in patients who had received psychostimulants previously and in those who had received no prior stimulant therapy [26]. The present study specifically addresses the clinical response to modafinil in patients treated previously with three psychostimulants (dextroamphetamine, methylphenidate, and pemoline). Patients included in this 6-week, open-label study had moderate-to-severe daytime sleepiness and experienced prior unsatisfactory treatment with stimulant medications.

2. Materials and methods

This study was conducted at 20 centers in the United States using a protocol approved by local ethics committees. Eligible patients were made aware of the potential benefits and risks of treatment with modafinil and provided written informed consent before entry into the study.

2.1. Subjects

Patients 18–68 years of age with a current diagnosis of narcolepsy in accordance with International Classification of Sleep Disorders criteria [27] participated in the study. All patients or their physicians reported dissatisfaction with psychostimulant treatment (i.e. dextroamphetamine, methylphenidate, or pemoline) taken to alleviate daytime sleepiness. Treatment with psychostimulants was considered to be unsatisfactory for one or more of the following reasons: low tolerability to side effects such as agitation, jitteriness, irritability, and mood swings; cardiovascular concerns such as palpitations, tachycardia, and increased blood pressure; concern about tolerance, dependence, or abuse potential; the need for drug holidays; dissatisfaction for other unspecified reasons. All patients were required to go through a 2-week washout period (see below) and have a negative urine drug screen before receiving modafinil.

Patients with a history of therapeutic failure to existing therapies for daytime sleepiness were excluded from study participation. Patients were also excluded if they had any active, clinically significant disorders of gastrointestinal, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, neurological (other than narcolepsy/cataplexy), respiratory, or psychiatric origin. Other exclusion criteria included hypertension, obstructive respiratory disease, glaucoma, psychiatric disorder, insulin-dependent diabetes, drug sensitivity or drug allergy to stimulant medications, or any prior experience with modafinil.

2.2. Study design

The study was a flexible-dose, open-label trial that included a 2-week washout period (5 days to taper off stimulants followed by 7–9 days without stimulants), followed by a 6-week period of treatment with modafinil. Patients were scheduled to visit the clinic five times during the course of the study: at screening (Day 14), at baseline after the 2-week washout period (Day 0), at the end of the first and second weeks of treatment (Weeks 1 and 2, respectively), and at the end of the study (Week 6) or at the termination visit.

During the first week of treatment, all patients received 200 mg of modafinil, supplied as 100-mg tablets for oral administration, to be taken as a single dose from 1 h before to 1 h after the morning meal. At the end of Week 1, the dose of modafinil could be increased to 400 mg at the discretion of the investigator, depending on efficacy and tolerability. At the end of the second week of treatment, the investigator determined the optimal daily dose of modafinil (i.e. 200 or 400 mg), which was taken for the remainder of the study (Weeks 2–6).

2.3. Assessments

The efficacy of modafinil was assessed using the Epworth Sleepiness Scale (ESS), a validated measure of subjective sleepiness [28]. ESS total scores ranged from 0 to 24. The ESS was administered at post-washout baseline and at the end of Weeks 1, 2, and 6.

Efficacy was further evaluated using Clinical Global Impression scales [29]. At the baseline visit, the severity of illness, in comparison to the narcoleptic patient population, was rated by independent clinicians using the Clinical Global Impression of Severity (CGI-S). Scores ranged from 1 ('normal') to 6 ('among the most extremely ill'). The Clinical Global Impression of Change (CGI-C) was used to assess the change in illness severity. Clinicians rated patients at the end of Weeks 1, 2, and 6. CGI-C scores ranged from 1 ('very much improved') to 7 ('very much worse').

To evaluate safety, all observed and reported adverse events were recorded throughout the study by type and day of onset. Adverse events that were observed or reported

during open-label treatment with modafinil (but not during the washout period) were considered to be treatment emergent. For each adverse event, investigators assigned a severity rating and assessed the relationship to study medication (i.e. not related, unlikely to be related, possibly related, probably related, or definitely related). Adverse events categorized as possibly, probably, or definitely related to study medication were considered to be treatment related.

A complete physical examination was conducted at the screening visit and at the end of the study. Blood and urine samples were collected for laboratory evaluation of clinical parameters (i.e. hematology, blood chemistry, and urinalysis) at the screening visit, the baseline visit, and at the end of the study. Vital signs (including sitting and standing blood pressure and pulse rates) were monitored at each clinic visit.

2.4. Statistical analysis

All patients who received at least one dose of modafinil and had at least one post-washout efficacy evaluation were included in the efficacy analyses. Patients were evaluated as a single population (i.e. all patients) and also by subgroup according to the stimulant medication taken most recently before entry into the study. For all patients and for patients in each subgroup, the mean changes from baseline in ESS scores at Weeks 1, 2, and 6 were analyzed using paired *t*-tests. Comparisons between subgroups were performed using an analysis-of-variance model with site and previous treatment as factors. CGI-C data were analyzed using the Wilcoxon signed-rank test for all patients and for each subgroup. Comparisons between prior-treatment subgroups were performed using the Cochran-Mantel-Haenszel test. Each test of treatment effect was two-sided and performed at a significance level of 5%.

3. Results

3.1. Baseline characteristics

A total of 151 patients who had been unsatisfactorily treated for excessive sleepiness associated with narcolepsy, as reported by themselves or their physicians, were enrolled in the study. Forty-eight patients (32%) were previously treated with dextroamphetamine, 66 patients (44%) were previously treated with methylphenidate, and 37 patients (25%) were previously treated with pemoline. Baseline characteristics of all patients and patients by prior-treatment

Table 1
Baseline characteristics of patients enrolled in the study[a]

Characteristic	All patients ($N = 151$)	Prior-treatment subgroup		
		DEX ($N = 48$)	MP ($N = 66$)	PEM ($N = 37$)
Mean age, year (range)	39 (18–68)	38 (18–68)	39 (18–67)	40 (18–66)
Gender, male/female; *N*	70/81	22/26	31/35	17/20
Mean weight, kg (SD)	81 (19)	80 (19)	80 (19)	85 (20)
Mean height, cm (SD)	172 (10)	172 (11)	172 (9)	172 (10)
Mean number of years since narcolepsy diagnosis (SD)	6.4 (9.3)	7.5 (10.8)	6.6 (10.1)	4.7 (4.7)
Mean post-washout baseline ESS score (SD)[b]	17.8 (4.4)	18.3 (4.3)	17.9 (4.9)	16.8 (3.6)
Baseline CGI-S, N (%)[c]				
Normal	5 (3)	2 (4)	2 (3)	1 (3)
Borderline ill	3 (2)	0	3 (5)	0
Slightly ill	18 (12)	4 (8)	9 (14)	5 (14)
Moderately ill	71 (47)	22 (46)	31 (47)	18 (50)
Markedly ill	49 (33)	17 (35)	20 (30)	12 (33)
Among the most extremely ill	4 (3)	3 (6)	1 (2)	0
Take drug holidays, *N* (%)	68 (45)	24 (50)	28 (42)	16 (43)
Reasons for taking drug holidays, *N* (%)				
Prevent tolerance	46 (68)	17 (71)	15 (54)	14 (88)
Side effects	30 (44)	12 (50)	14 (50)	4 (25)
Not needed all the time	12 (18)	1 (4)	8 (29)	3 (19)
Afraid of addiction	8 (12)	2 (8)	2 (7)	4 (25)
Expense	8 (12)	4 (17)	2 (7)	2 (13)

[a] Abbreviations: DEX = dextroamphetamine, MP = methylphenidate, and PEM = pemoline.
[b] ESS scores were available for 65 of 66 patients who previously received methylphenidate.
[c] CGI-S ratings were available for 36 of 37 patients who previously received pemoline.

subgroups are summarized in Table 1. Of the 150 patients who received a CGI-S no-treatment baseline rating (one patient did not receive a CGI-S assessment), 124 patients (83%) were considered to be moderately ill, markedly ill, or among the most extremely ill. The mean ESS (SD) score after the initial washout period was 17.8 ± 4.4, which corroborated the clinicians' initial evaluations of disease severity and indicated a return to pathologic levels of daytime sleepiness when treatment with psychostimulants was discontinued.

3.2. Previous stimulant treatment

Sixty-eight patients (45%) reported discontinuing their previous psychostimulant medication for short periods of time (i.e. took drug holidays). Of the 68 patients who took drug holidays, 76% indicated that the average length of each holiday was 1 or 2 days. Sixty-eight percent (68%) of patients who took drug holidays indicated that they did so to forestall tolerance or to prolong the effectiveness of the medication (Table 1).

3.3. Patient disposition

All 151 patients successfully completed a 2-week washout from their prior stimulant and were treated with modafinil. A total of 123 patients (82%) completed the study; the percentages of patients completing the study were similar among the prior-treatment subgroups (approximately 80%). Eight patients (5%) discontinued the study because of insufficient efficacy. Of these patients, two had received dextroamphetamine previously, two patients had received methylphenidate, and four patients had received pemoline. Nine patients (6%) discontinued the study because of one or more adverse clinical events; in five patients (3%), the adverse events leading to discontinuation were considered by the investigator to be related to treatment. Two of the five patients had received dextroamphetamine previously and three had received methylphenidate. Other reasons for study discontinuation included abnormal laboratory test results ($N = 1$), protocol violation ($N = 1$), withdrawn consent ($N = 4$), non-compliance ($N = 1$), lost to follow up ($N = 1$), and other ($N = 3$).

3.4. Dosing

The percentages of patients receiving 200- or 400-mg doses of modafinil at Weeks 1, 2, and 6 are shown in Fig. 1. During the first week of the study, the majority of patients (95%) received 200 mg of modafinil, the protocol-specified daily dose. For most patients, a change in dosing was implemented at the investigator's discretion at the end of Week 1. During Week 2, 105 of 139 patients (70%) were receiving once-daily doses of 400 mg of modafinil. At the end of the study (Week 6), 109 of 145 patients (75%) were receiving 400 mg of modafinil, and 34 patients (23%) were receiving 200 mg of modafinil.

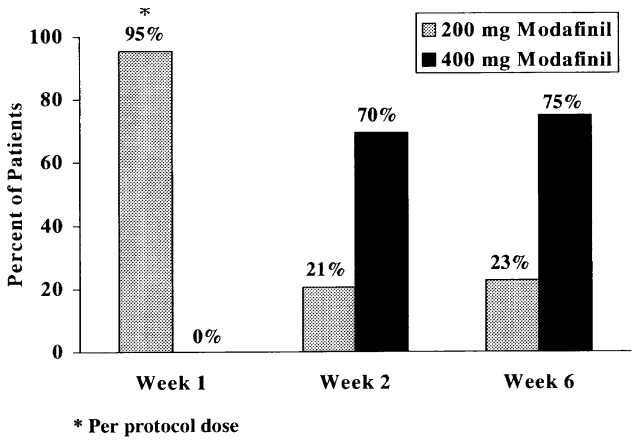

Fig. 1. Percentage of patients receiving 200- or 400-mg daily doses of modafinil during 6 weeks of open-label treatment. Note: some patients received doses of modafinil other than 200 or 400 mg. These were: at Week 1, 100 mg, $N = 4$; at Week 2, 300 mg, $N = 3$; and at Week 6, 300 mg, $N = 1$ and 800 mg, $N = 1$.

3.5. Efficacy outcomes

Modafinil significantly improved wakefulness compared with post-washout baseline as early as Week 1, with improvements in wakefulness maintained for the duration of the study (all $P < 0.001$) (Fig. 2). The mean ESS (SEM) score for all patients at Week 1 was 12.7 (0.5). The mean ESS (SEM) score at Week 6 was 11.8 (0.5). When patients were categorized by the stimulant medication taken prior to study entry, mean baseline scores were similar among the prior-treatment subgroups. Significant improvements ($P < 0.001$) from baseline in wakefulness were demonstrated for each subgroup. No significant differences in the mean change from baseline in ESS scores were shown among the subgroups at any post-baseline time point.

Clinicians rated the majority of patients receiving modafinil as clinically improved relative to post-washout baseline. Significant improvements in medical condition were shown at Week 1, with improvements maintained for the duration of the study (all $P < 0.001$ versus baseline). Overall, 86% (125/145) of all patients were reported to be clinically improved (i.e. minimally improved, much improved, or very much improved) after 1 week of treatment with modafinil (Fig. 3). At Weeks 2 and 6, 90% (121/135) and 79% (111/141), respectively, of all patients were considered to be clinically improved. Over the course of the study, the percentage of patients who experienced a worsening of illness severity ranged from 3 to 7%. Improvements in medical condition were demonstrated regardless of the stimulant medication taken previously. No significant differences in mean CGI-C scores were observed among the prior-treatment subgroups at any post-baseline time point.

3.6. Safety outcomes

All patients who received at least one dose of modafinil

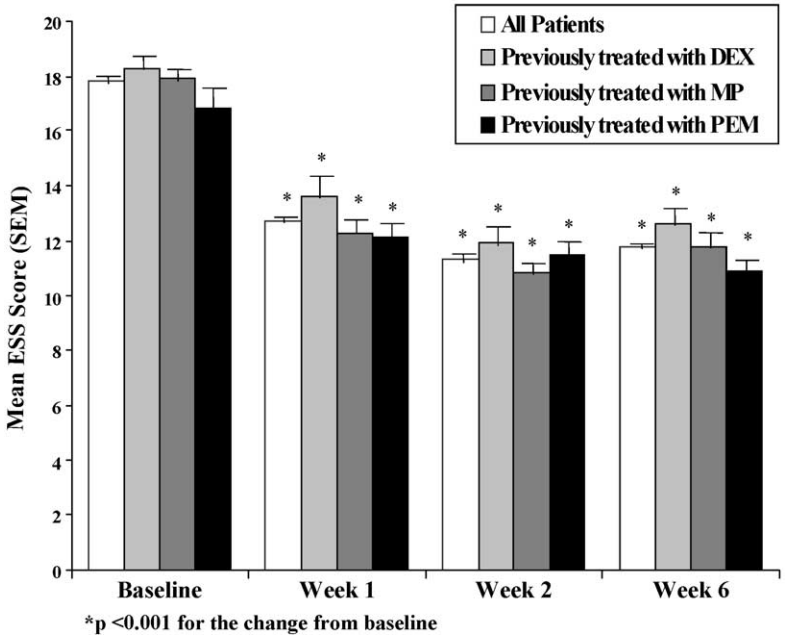

Fig. 2. Mean (SEM) ESS scores at baseline and during 6 weeks of treatment with modafinil. DEX = dextroamphetamine; MP = methylphenidate; and PEM = pemoline.

were included in the safety analysis. During the 2-week stimulant washout period, 42 of the 151 patients (28%) experienced an adverse event. The most common adverse events were headache or migraine (7%), infection (4%), nervousness (2%), somnolence (2%), and bronchitis (2%). Almost all (98%) of these adverse events were mild or moderate in nature, and no patient withdrew from the study prior to receiving modafinil treatment. During the 6-week modafinil treatment period, the most common treatment-emergent adverse events were headache (35%), nausea (10%), and insomnia (9%) (Table 2). The majority of treatment-emergent adverse events (93%) were mild or moderate in nature. There were no serious adverse events during the study. Among the prior-treatment subgroups,

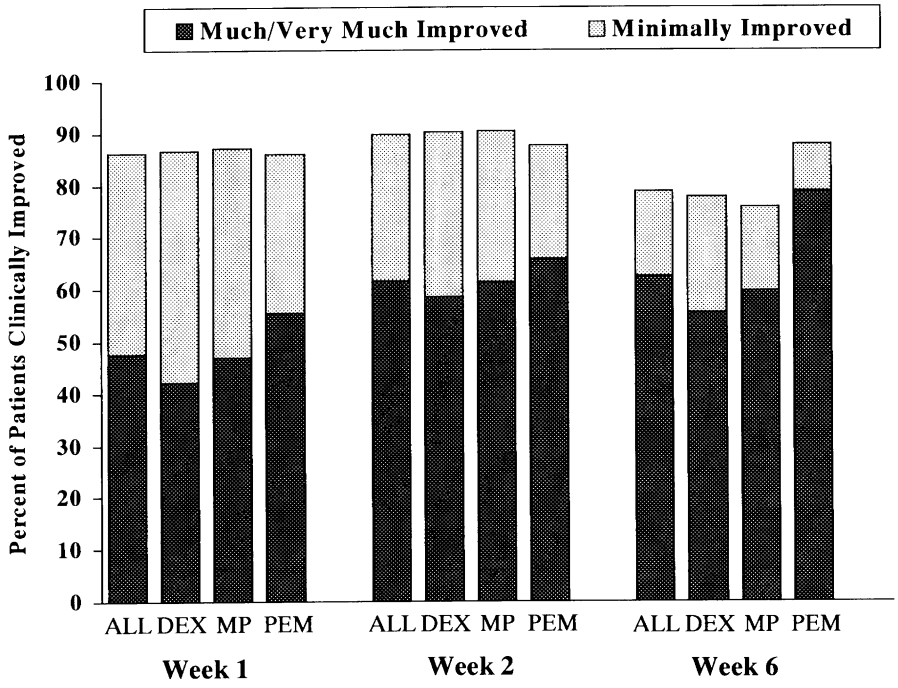

Fig. 3. Percentage of patients with improvements in CGI-C ratings. ALL = all patients; DEX = dextroamphetamine; MP = methylphenidate; and PEM = pemoline.

Table 2
Most frequently occurring treatment-emergent adverse events during 6 weeks of modafinil treatment[a]

Adverse event	No. of patients (%)	Mild	Moderate	Severe
Headache	53 (35)	32	16	5
Nausea	15 (10)	13	1	1
Insomnia	13 (9)	7	4	2
Infection	12 (8)	7	5	0
Nervousness	10 (7)	8	2	0
Dry mouth	10 (7)	9	0	1
Diarrhea	9 (6)	8	1	0
Rhinitis	9 (6)	3	0	9
Pharyngitis	8 (5)	7	0	1

[a] Adverse events that occurred in ≥5% of patients (total $N = 151$). If a patient reported an adverse event more than once during the treatment period, the greatest known severity is presented.

treatment-emergent adverse events were similar in type, incidence, and attribution to treatment.

Five patients (3%) discontinued the study because of one or more adverse events considered to be related to treatment. The treatment-related adverse events leading to discontinuation were headache ($N = 3$), abnormal thinking ($N = 2$), depression ($N = 2$), dizziness ($N = 1$), nausea ($N = 1$), asthenia ($N = 1$), and anxiety ($N = 1$). For all patients, the mean changes from baseline in laboratory test results and vital signs (including sitting and standing systolic blood pressure, sitting or standing diastolic blood pressure, and heart rate) were generally small and not clinically significant.

4. Discussion

Following a 2-week washout period and a return to pathological levels of daytime sleepiness, treatment with modafinil significantly improved wakefulness and overall clinical condition compared with post-washout baseline in narcolepsy patients who had been unsatisfactorily treated with psychostimulants. The beneficial effects of modafinil were demonstrated as early as Week 1 and were maintained through 6 weeks of treatment. The improvements in wakefulness from post-washout baseline levels were similar regardless of the type of psychostimulant used previously to control daytime sleepiness. The majority of patients required more than the recommended daily dose of 200 mg, with >70% requiring treatment with the 400 mg daily dose.

The improvements in wakefulness following the initiation of treatment with modafinil in this 6-week, open-label study are similar to those obtained in two 9-week, double-blind, placebo-controlled studies of modafinil for the treatment of daytime sleepiness in 558 patients with narcolepsy [12,13]. Moreover, analysis of data from these trials demonstrated that there was no statistically significant difference in mean ESS scores between patients who had received prior treatment with stimulants and those who had not [26]. The results of the present study demonstrate that post-treatment scores for daytime wakefulness in patients treated previously with psychostimulants were improved and as low as those reported for patients who are newly diagnosed or naïve to treatment.

The improvements in overall clinical condition following open-label treatment with modafinil are also similar to those reported previously in up to 88 weeks of long-term follow-up [15,22]. In these previous studies, the majority of patients (approximately 80%) were rated as clinically improved. In the current study, there was some decline in the percentage of patients who were rated as at least minimally improved between Weeks 2 and 6 (90 and 79%, respectively). This may suggest that some patients may not have had a sustained response to modafinil. Nevertheless, the findings that approximately 80% of patients are clinically improved is consistent with previous reports of sustained efficacy with much longer term treatment (i.e. up to 88 weeks in measures of clinical condition [22] and as long as 136 weeks for subjective sleepiness [21]).

Few patients discontinued from modafinil treatment due to insufficient efficacy (5%), with a rate similar to those reported in large-scale, placebo-controlled clinical trials [10,12,13]. However, two case-series studies have reported that some patients encounter difficulties when switching to modafinil [25,30]. In one case-series study, patients who previously received dextroamphetamine were less successful at switching to modafinil in comparison to those taking pemoline or methylphenidate [25]. In another, the authors noted that patients who required relatively high doses of methylphenidate (≥70 mg daily) were less likely to continue with modafinil therapy [30].

An expectation of arousal or euphoriant effects in addition to simple wake promotion may also explain why some patients with a history of prior psychostimulant treatment may be unable or reluctant to switch to modafinil, which promotes wakefulness but is not associated with arousal or euphoria. In the present study, the reductions in mean ESS scores from post-washout baseline levels suggest that the majority of patients were able to distinguish between improved wakefulness attributable to modafinil and euphoriant effects that may occur with psychostimulant use. This is consistent with the findings that subjects receiving amphetamine experienced increased arousal and commented on their improved well being, while subjects receiving modafinil were less fatigued or sleepy and were neutral in comments made relative to affect [31].

The findings must be considered within the limitations of the study design. The study was not intended to compare the efficacy of modafinil with that of the stimulants for improving daytime wakefulness. We do not know how many of these patients continued modafinil treatment beyond the study period. The current study featured an open-label design and incorporated only subjective measures of efficacy. Nevertheless, the results were consistent with previous studies in narcolepsy patients employing objective

measures. The results of this study suggest that modafinil may be an effective and well-tolerated treatment for improving daytime wakefulness in patients with narcolepsy who were previously treated with psychostimulants.

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