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Original article

Long-term efficacy and safety of modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy

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Abstract

Objectives: To assess the long-term efficacy and safety of modafinil in patients with excessive daytime sleepiness (EDS) associated with narcolepsy.

Background: Modafinil has been shown to be effective and well tolerated for treating EDS associated with narcolepsy in two large-scale, well-controlled, 9-week clinical trials.

Methods: Four hundred and seventy eight adult patients with a diagnosis of narcolepsy who had completed one of two 9-week, double-blind, placebo-controlled, multicenter, clinical trials of modafinil were enrolled in two 40-week, open-label, extension studies. A flexible-dose regimen (i.e. 200, 300, or 400 mg daily) was followed in one study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week. Investigators then prescribed either 200- or 400-mg doses for the duration of the study. Efficacy was evaluated using Clinical Global Impression of Change (CGI-C) scores, the Epworth Sleepiness Scale (ESS), and the 36-item Medical Outcomes Study health survey (SF-36). Adverse events were recorded. Data from the two studies were combined.

Results: The majority of patients (~75%) received 400 mg of modafinil daily. Disease severity improved in >80% of patients throughout the 40-week study. At weeks 2, 8, 24, and 40, disease severity was 'much improved' or 'very much improved' in 49, 58, 59, and 58% of patients, respectively. The mean (±SEM) ESS score improved significantly from 16.5 ± 0.2 at open-label baseline to 12.4 ± 0.2 at week 2 and remained at that level through week 40 ($P < 0.001$). Quality of life scores at weeks 4, 8, 24, and 40 were significantly improved versus open-label baseline scores for six of the eight SF-36 domains ($P < 0.001$). The most common treatment-related adverse events were headache (13%), nervousness (8%), and nausea (5%). Most adverse events were mild to moderate in nature. A total of 341 patients (71%) completed the studies. Forty-three patients (9.0%) discontinued treatment because of adverse events.

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Conclusions: Modafinil is effective for the long-term treatment of EDS associated with narcolepsy and significantly improves perceptions of general health. Modafinil is well tolerated, with no evidence of tolerance developing during 40 weeks of treatment.

Keywords: Modafinil; Narcolepsy; Sleep disorders; Wakefulness; Quality of life; Disorders of excessive somnolence

1. Introduction

Narcolepsy affects 0.03–0.06% of the population in North America and Western Europe [1]. Although this disorder is sometimes inherited [2,3], the etiology of narcolepsy is unknown and there is no known cure. The hallmark characteristics of narcolepsy include a tetrad of symptoms (excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations) that may present at different times of life. Of these symptoms, EDS and sudden sleep attacks are the most common complaints and are largely responsible for the overall disruption of the normal daytime functioning of patients with narcolepsy [4–6]. In order to function adequately during the day, most patients depend on chronic, daily dosing with central nervous system (CNS) stimulants, such as methylphenidate, dextroamphetamine, methamphetamine, and pemoline [7,8]. However, CNS stimulants are often associated with significant adverse side effects and are sometimes not effective in long-term treatment [9,10]. Furthermore, CNS stimulants (except pemoline) are associated with a significant abuse potential in the general population [8–10] and have been placed in Schedule II of the Controlled Substances Act. Pemoline, which is considered to have a lower abuse potential, has been classified as a Schedule IV drug.

Modafinil, a novel wake-promoting agent, was approved by the U.S. Food and Drug Administration in December 1998 for the treatment of EDS associated with narcolepsy. Although modafinil has wake-promoting actions in common with CNS stimulants, its pharmacological profile differs from that of traditional CNS stimulants, making it an attractive alternative to existing pharmacological treatments for EDS associated with narcolepsy. Modafinil has demonstrated psychoactive effects that are similar in some respects to those of traditional CNS stimulants, and has been listed in Schedule IV. Although modafinil has been available in parts of Europe for several years, more recent large-scale clinical studies conducted in the United States have confirmed that modafinil is effective in promoting wakefulness and well tolerated in patients with narcolepsy. Specifically, the efficacy and safety of modafinil were demonstrated in two 9-week, multicenter, double-blind, placebo-controlled, fixed-dose trials [11,12], which were the largest trials (enrolling more than 500 patients) conducted in narcolepsy. Daily treatment with 200 or 400 mg of modafinil resulted in significant improvement in the results of two standard objective tests of EDS conducted in controlled sleep laboratory settings: the multiple sleep latency test (MSLT) [13] and the maintenance of wakefulness test (MWT) [14]. The clinician-evaluated Clinical Global Impression of Change (CGI-C) scores [15] also indicated that the severity of disease was reduced in 58–74% of patients receiving treatment with modafinil compared with 37–38% of patients receiving placebo [11,12]. In addition, patients reported a significant reduction in the likelihood of dozing in several common situations of daily living, as measured by the Epworth Sleepiness Scale (ESS) [16]. One trial included a 2-week, double-blind, withdrawal phase. As expected, discontinuation of modafinil resulted in a return of sleepiness [11]. However, patients did not experience a pattern of withdrawal-emergent adverse events, suggesting that dependence did not develop during 9 weeks of daily treatment with modafinil at therapeutic levels. The present analysis assesses the long-term efficacy and safety of daily modafinil for the treatment of EDS in patients with narcolepsy during two 40-week, open-label extension studies.

2. Methods

2.1. Patients

Men and women were eligible for inclusion in the 40-week, open-label studies if they had a diagnosis of

narcolepsy according to the International Classification of Sleep Disorders (ICSD) criteria [17] and had completed one of two 9-week, double-blind, placebo-controlled, multicenter, clinical trials of modafinil conducted in the United States [11,12]. Patients also were eligible for enrollment in the open-label studies if they had withdrawn from one of these two double-blind studies after completing at least two post-baseline evaluations of efficacy, but withdrew from the study for reasons other than treatment-related adverse events or non-compliance. The two double-blind studies included an 18-center trial and a 21-center trial. Patients were required to be 18–65 years of age at entry into the double-blind studies.

The ICSD definition of narcolepsy is comprised of two sets of minimum diagnostic criteria. The first (criteria A) requires documentation of recurrent daytime naps or lapses into sleep that occur almost daily for a period of at least 3 months plus a history of cataplexy (defined as a sudden bilateral loss of postural muscle tone in association with intense emotion). The second (criteria B) requires documentation of complaints of excessive sleepiness or sudden muscle weakness plus associated features (such as, sleep paralysis, hypnagogic hallucinations, automatic behaviors, or disrupted major sleep episode) plus abnormal sleep test results detected by polysomnography. Abnormal sleep test results during polysomnography are defined as documentation of at least one of the following: (1) sleep latency of $<$10 min, (2) rapid eye movement (REM) sleep latency of $<$20 min, (3) a mean MSLT sleep latency of $<$5 min, and (4) two or more sleep-onset REM periods.

For inclusion in either of the two 9-week, double-blind studies, patients who met criteriaA of the ICSD definition of narcolepsy also were required to have a mean MSLT score of $\leq$8 min, and patients who met criteria B of the ICSD definition of narcolepsy also were required to have a mean MSLT score of $\leq$5 min. Patients were included in the double-blind trials only if they had discontinued treatment with drugs or substances with psychotropic effects (including stimulants) for at least 14 days before the baseline evaluation.

Patients were excluded from study participation if they had a history of adverse reactions to CNS stimulants or active, clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, neurological (other than narcolepsy/cataplexy), respiratory, or psychiatric disorders. Additionally, patients with cataplexy who were unable or unwilling to temporarily discontinue anticataplectic medication were excluded from the double-blind studies.

All candidates who were eligible for inclusion in the double-blind studies were informed of the potential benefits and risks of treatment with modafinil and signed an institutional review board-approved informed consent form before receiving study medication (i.e. placebo or modafinil). Having signed informed consent forms prior to entry into the double-blind studies, patients were not required to provide informed consent on entry into the open-label phase of the two studies.

2.2. Study designs

All patients eligible for enrollment in the 40-week, open-label extension of the 18-center study underwent a 2-week washout period, during which they received placebo in a blinded fashion. All patients who were in the placebo-treatment group of the 21-center study and who were eligible for enrollment in the 40-week, open-label extension trial underwent a 2-week washout period and continued to receive placebo. Approximately 80% of eligible patients in the 200- and 400-mg modafinil treatment groups of the 21-center study (predetermined at randomization into the 9-week, double-blind trials) also underwent a 2-week washout period and received placebo in a blinded fashion. Approximately 20% of patients receiving modafinil continued to receive modafinil (blinded) at their double-blind dose levels and did not undergo any washout period. The washout protocol for the 21-center study was designed to determine whether rebound EDS and/or withdrawal syndrome occurred in patients who discontinued treatment with modafinil when compared with EDS in patients who continued to receive modafinil. The results of the washout phase of the 21-center study have been reported elsewhere [12].

Clinic visits for both 40-week studies were scheduled at baseline and after 1, 2, 4, 8, 16, 24, and 40 weeks of treatment. At baseline, patients received a complete physical examination, including routine clinical laboratory tests, urine drug screens, 12-lead

electrocardiograms, and the measurement of vital signs. Severity of disease was also assessed using the Clinical Global Impression of Severity (CGI-S) scale [15].

The two open-label studies used different treatment protocols. The 40-week, open-label, extension of the 18-center, double-blind study followed a flexible-dose format, whereas the 40-week, open-label, extension of the 21-center, double-blind study followed an optimal, fixed-dose format. At the start of the 18-center, open-label study, all patients received a daily dose of 200 mg of modafinil. Thereafter, the daily dose of modafinil could be increased or decreased in 100-mg increments at the discretion of the investigator, depending on efficacy and tolerability. The range of daily doses permitted was 200–400 mg. At the start of the 21-center, 40-week, open-label study, all patients were assigned to treatment with 200-mg doses of modafinil daily for 1 week, followed by treatment with 400-mg doses of modafinil daily for 1 week. At the end of this 2-week treatment period, the study investigator determined the optimum dose of modafinil (i.e. 200 or 400 mg) based on efficacy and tolerability and assigned the patient to receive the optimum dose for the duration of the 40-week study. Investigators were instructed not to further adjust the daily dose of modafinil except to improve tolerability.

2.3. Efficacy assessments

Efficacy was assessed using the physician-evaluated CGI-C scale [15] and the patient's evaluation of EDS as scored using the ESS [16]. The CGI-C and ESS were administered at baseline and at weeks 2, 8, 24, and 40 in both 40-week studies. Quality of life (QoL) assessments were performed at baseline and weeks 4, 8, 24, and 40 using the 36-item Medical Outcomes Study short-form health survey (SF-36) [18–20]. The CGI-C score reflects the investigator's assessment of clinical improvement or worsening in the severity of disease. CGI-C scores range from 1 ('very much improved') to 7 ('very much worse'). The ESS, a measure of self-reported sleepiness, asks patients to rate the likelihood of dozing in eight common situations of daily living (e.g. sitting and reading, watching television, and while stopped in a car for a few minutes in traffic). Each question is scored from 0 ('would never doze') to 3 ('high chance of dozing'). Total ESS scores range from 0 to 24, and scores of $\leq$10 are typical for patients in the normal population without a history of EDS. The SF-36 is a generic measure of health-related QoL that is not age, disease, or treatment specific, and has been widely used as an indicator of treatment outcomes from the patient's perspective. Responses to the SF-36 are grouped into eight standardized domain (or subscale) scores: (1) bodily pain, (2) general health, (3) mental health, (4) physical functioning, (5) role emotional, (6) role physical, (7) social functioning, and (8) vitality. Two metascale scores also can be determined from the SF-36: the physical component summary score and the mental component summary score. Scores for the eight domains and the two metascales range from 0 to 100, with higher scores indicating a better health status.

2.4. Safety assessments

Data on adverse events (any cause) were collected throughout the study. Investigators were asked to assess whether the adverse event was most likely unrelated, remotely related, possibly related, probably related, or definitely related to study medication. For the safety analysis presented in this report, treatment-related adverse events were considered to be those events possibly, probably, or definitely related to study medication. Investigators also rated the severity of each adverse event as mild (no limitations of usual activities), moderate (some limitation of usual activities), or severe (inability to carry out usual activities). Serious adverse events were defined to be those that (1) were fatal, (2) were life-threatening, (3) were temporarily or permanently disabling, (4) led to or prolonged in-patient hospitalization, (5) were the result of overdose, or (6) resulted in a congenital anomaly. Additional safety measures included clinical laboratory tests (hematology, blood chemistry, and urinalysis), measurement of vital signs (including body weight), and 12-lead ECGs.

2.5. Statistical analysis

Data from the two 40-week, open-label extension studies were combined to obtain a single dataset. The data from the intention-to-treat study population were analyzed using a conservative last-observation-carried-forward (LOCF) algorithm to supply data

not collected at a particular study visit or to impute data for patients who discontinued treatment during the trials. The LOCF approach was used to minimize the potential for introducing a favorable bias into the efficacy analysis, which can occur when patients discontinue a study due to insufficient efficacy and data is only available for patients who respond favorably to treatment. The CGI-C scores obtained at weeks 8, 24, and 40 from the intention-to-treat population were compared with the CGI-C scores obtained at week 2 by determining the percentage of patients who were 'much improved' or 'very much improved' from open-label baseline and applying McNemar's test at the $P < 0.05$ level of significance. CGI-C scores were also assessed in the per-protocol population (i.e. only those patients who had an efficacy evaluation at the different study time points). The mean changes in total ESS scores from open-label baseline at weeks 2, 8, 24, and 40 were evaluated in the intention-to-treat study population using a two-tailed paired *t*-test at the $P < 0.05$ level of significance.

3. Results

3.1. Patients

A total of 478 of the 554 patients (86%) enrolled in the double-blind trials entered the 40-week, open-label studies: 238 were from the 18-center, double-blind study and 240 were from the 21-center, double-blind study. All patients were included in the safety analysis. One patient was excluded from the efficacy analysis due to a protocol violation. Patient demographics at open-label baseline are presented in Table 1. The patients were 18 to 68 years of age at the time of entry into the 40-week studies and 75% were considered to be moderately to markedly ill. All patients reported EDS associated with narcolepsy, and 60–95% of patients also reported the presence of other symptoms typically associated with narcolepsy. While most patients reported that the treatment they were receiving prior to entry into the 9-week double-blind studies was effective, approximately one in four patients reported that their prior medication was ineffective in controlling the symptoms of narcolepsy.

3.2. Modafinil dosing

The majority of patients (98%) started the open-label studies at the per-protocol dose of 200 mg of modafinil per day, but the dosing pattern changed markedly during the 40 weeks of treatment (Fig. 1). At the week 2 visit, the majority of the patients enrolled from the 21-center study were receiving the per-protocol dose of 400 mg daily. Twenty-eight percent of the patients, most of whom were from the 18-center study, were receiving 300-mg doses of modafinil, and only 18% of all patients were still

Table 1
Baseline characteristics of the patients entering the 40-week, open-label studies

Characteristic	
No. of patients	478
Age (mean ± SD) (years)	42 ± 13
Age range (years)	18–68
Sex; % male:% female	46:54
Epworth sleepiness scale score (mean ± SD)	16.5 ± 4.6
Clinical global impression of severity; n (%)[a]	
Borderline ill	16 (3.4)
Slightly ill	73 (15.7)
Moderately ill	197 (42.4)
Markedly ill	152 (32.8)
Among the most extremely ill	26 (5.6)
Narcolepsy symptoms; n (%)	
Excessive daytime sleepiness	474 (99.2)
Daytime sleep attacks	455 (95.2)
Cataplexy	384 (81.0)
Interrupted sleep	348 (72.8)
Hypnagogic hallucinations	310 (64.9)
Sleep paralysis	285 (59.8)
Treatment history; n (%) answering 'yes'	
Instructed to take drug holidays	174 (37.1)
Found medication to be ineffective	98 (24.6)
Switched drugs frequently	26 (5.5)
Race; n (%)	
Caucasian	396 (82.9)
Black	65 (13.6)
Hispanic	13 (2.7)
Other	4 (0.8)

[a] Open-label baseline scores were available for 464 of 478 patients.

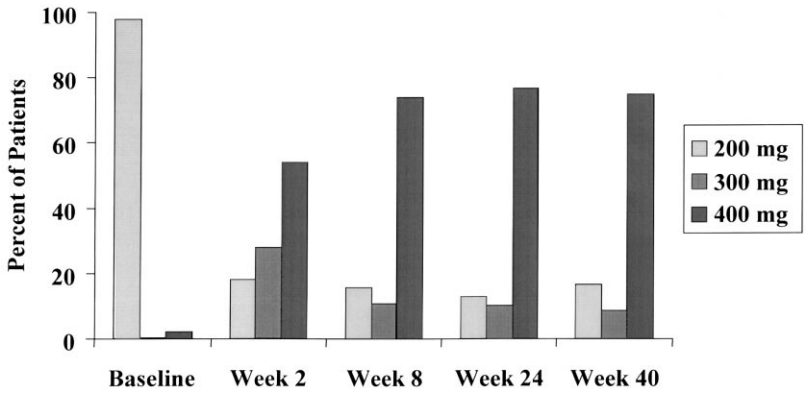

Fig. 1. Distribution of modafinil doses during the 40-week, open-label studies. At baseline, all patients (with a few exceptions) received starting doses of 200 mg of modafinil according to protocol. Doses for patients in the 18-center study ($N = 238$) could be adjusted throughout the study in 100-mg increments over the range of 200–400 mg. In the 21-week study, patients ($N = 240$) received 200 mg daily for the first week and 400 mg daily for the second week according to protocol. At the week 2 visit, patients in the 21-center study were assigned to receive daily doses of either 200 or 400 mg of modafinil for the duration of the study, based on the investigator's assessment of efficacy and tolerability.

receiving 200-mg doses. The week 8 visit was the first clinic visit for which none of the patients was restricted by protocol to receive a particular dose of modafinil. At the week 8 visit, the majority of patients (74%) were receiving 400-mg doses of modafinil daily and only 15% were receiving 200-mg doses. This dose distribution was largely maintained for the remainder of the open-label studies, with 75% of patients receiving 400-mg doses at week 40 and 16% receiving 200-mg doses.

3.3. Efficacy

Treatment with modafinil during the 40-week study resulted in significant clinical improvement in the severity of disease for the majority of patients, with the effects of treatment evident as early as week 2, the first visit at which efficacy assessments were performed. At the week 2 visit, 394 of 477 patients (83%) in the intention-to-treat population had an improvement in disease severity from open-label

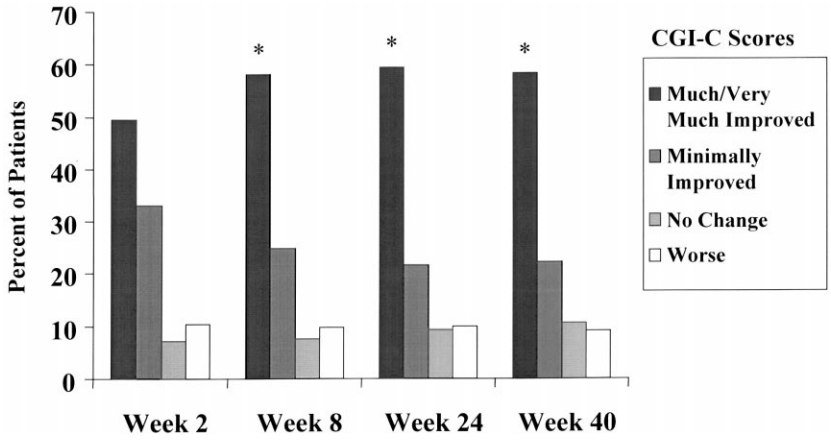

Fig. 2. Distribution of patients in the intention-to-treat population by CGI-C score at weeks 2, 8, 24 and 40 ($N = 477$). *$P < 0.001$ vs. week 2.

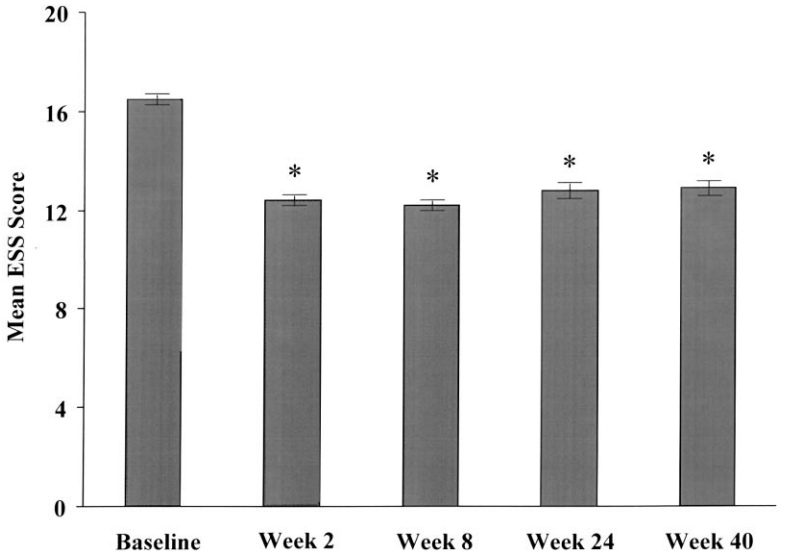

Fig. 3. Mean (±SEM) Epworth Sleepiness Scale (ESS) scores at baseline and at weeks 2, 8, 24, and 40 of the open-label studies for the intention-to-treat population ($N = 471$). *$P < 0.001$ for mean change from open-label baseline.

baseline, as measured by CGI-C scores (Fig. 2). The percentage of patients who had an improvement in disease severity remained essentially constant (81% to 83%; $N = 477$) throughout the 40-week study. CGI-C scores indicated no change in disease severity in 7–10% of patients and a worsening of symptoms in 9–10% of patients.

A total of 236 of 477 patients (49%) in the intention-to-treat population were considered 'much improved' or 'very much improved' at week 2 (Fig. 2). The percentage of patients considered to be 'much improved' or 'very much improved' increased significantly to 58, 59, and 58%, respectively, at weeks 8,

Table 2
Mean SF-36 domain and metascale scores at open-label baseline and at week 4 and week 40 of treatment with modafinil[a]

SF-36 Scale	Open-label Baseline		Week 4		Week 40	
	N	Mean ± SEM	*N*	Mean ± SEM	*N*	Mean ± SEM
BP	447	75.0 ± 1.1	473	74.4 ± 1.1	473	73.5 ± 1.1
GH	438	68.5 ± 1.0	470	69.9 ± 1.0	473	68.8 ± 1.0
MH	446	68.0 ± 0.9	473	70.6 ± 0.8	473	70.3 ± 0.9
PF	446	76.8 ± 1.2	473	80.1 ± 1.1	473	80.1 ± 1.1
RE	441	61.2 ± 2.0	472	68.7 ± 1.9	473	68.0 ± 1.8
RP	444	40.8 ± 1.9	472	59.7 ± 1.9	473	54.9 ± 1.9
SF	449	64.5 ± 1.4[b]	473	72.6 ± 1.3	473	71.6 ± 1.2
VT	447	32.6 ± 1.1	473	47.0 ± 1.1	473	45.6 ± 1.1
PCS	432	45.5 ± 0.5	469	47.6 ± 0.5	473	46.8 ± 0.5
MCS	432	42.4 ± 0.6	469	45.6 ± 0.5	473	45.4 ± 0.5

[a] Abbreviations: BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role functioning – emotional; RPm role functioning – physical; SF, social functioning; VT, vitality; PCS, physical component summary; MCS, mental component summary.

[b] The mean change (±SEM) from double-blind baseline was 4.4 ± 1.2 and was statistically significant ($P < 0.05$). The mean changes in scores from double-blind baseline to open-label baseline for the other SF-36 domain and metascale parameters ranged from −0.3–1.9 and were not significant.

24, and 40 ($P < 0.001$ vs. week 2 at all time points; $N = 477$).

Of the patients who had an efficacy evaluation at the study time point, 52% (236 of 455) were considered 'much improved' or 'very much improved' at week 2. The percentages of patients considered to be 'much improved' or 'very much improved' at subsequent study visits were 63% (269 of 430) at week 8, 69% (255 of 371) at week 24, and 72% (241 of 335) at week 40.

Self-reported sleepiness, as determined by mean ESS scores at baseline and at weeks 2, 8, 24, and 40, is presented in Fig. 3. Because of the 2-week washout phase following the 9-week, double-blind studies, patients who were withdrawn from modafinil treatment experienced a return to baseline in ESS scores (mean (SEM) 16.5 (0.2), median 17). Following initiation of treatment with modafinil, the mean decreases in ESS scores from open-label baseline were highly significant ($P < 0.001$) at weeks 2, 8, 24, and 40. The mean total scores at all time points after baseline were between 12.2 and 12.9. The median score was 12 at weeks 2, 8, and 24 and 13 at week 40.

Mean scores for the eight domains and the two metascales of the SF-36 at baseline and weeks 4 and 40 of open-label treatment are presented in Table 2. Mean scores at baseline of the open-label studies were not statistically different from mean scores at baseline of the double-blind studies for any of the ten SF-36 parameters, except for the social functioning domain. After 4 weeks of treatment with modafinil, the mean SF-36 scores were higher for seven of the eight domains (except bodily pain) and for both the physical and mental health metascales; these improvements in absolute scores from baseline were maintained through week 40 of the study.

The mean changes in SF-36 scores from open-label baseline at weeks 4 and 40 were statistically significant ($P < 0.001$) for six of the eight domain scores and for the physical and mental health metascores (Fig. 4). The greatest increases in scores were observed for the following domains: role physical, vitality, social functioning, and role emotional.

3.4. Safety

The most common adverse events of any cause occurring in 5% or more of patients are presented in Table 3, and the most common treatment-related adverse events occurring in 2.5% or more of patients are presented in Table 4. The most common adverse events of any cause were headache (43%), infection (24%), rhinitis (14%), dyspepsia (13%), pain (13%),

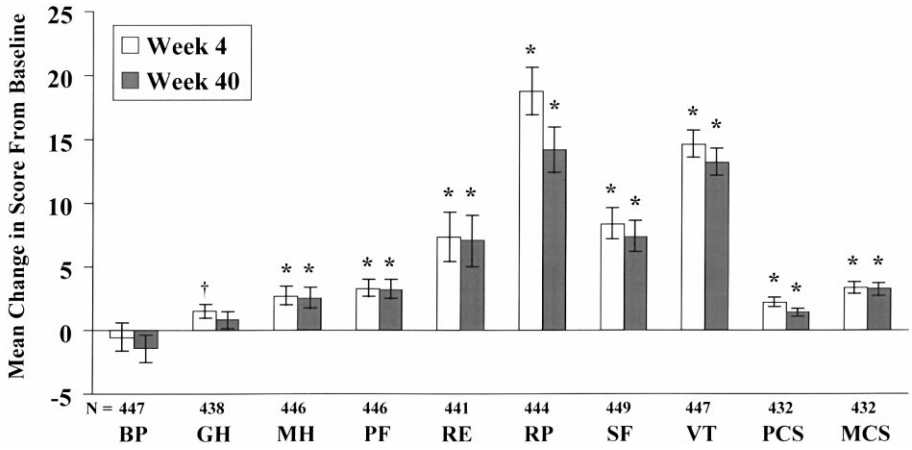

Fig. 4. Mean change (±SEM) from open-blind baseline at week 4 (white bars) and week 40 (gray bars) for the eight domains and two metascales of the SF-36. Abbreviations: BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role functioning – emotional; RP, role functioning – physical; SF, social functioning; VT, vitality; PCS, physical component summary; MCS, mental component summary. † $P < 0.05$ vs. open-label baseline. *$P < 0.001$ vs. open-label baseline.

Table 3
Incidence of adverse events of any cause reported by ≥5% of patients

Adverse event (AE)	All patients ($N = 478$)[a]		Dose of modafinil when the AE occurred[b]					
			200 mg ($N = 147$)		300 mg ($N = 163$)		400 mg ($N = 388$)	
	N	%	*N*	%	*N*	%	*N*	%
Headache	204	42.7	51	34.7	55	33.7	142	36.6
Infection	113	23.6	22	15.0	12	7.4	86	22.2
Rhinitis	66	13.8	9	6.1	15	9.2	49	12.6
Dyspepsia	62	13.0	13	8.8	13	8.0	45	11.6
Pain	60	12.6	9	6.1	14	8.6	44	11.3
Tooth disorder	55	11.5	7	4.8	15	9.2	35	9.0
Nausea	52	10.9	13	8.8	14	8.6	30	7.7
Nervousness	44	9.2	15	10.2	19	11.7	23	5.9
Sinusitis	38	7.9	10	6.8	8	4.9	25	6.4
Accidental injury	37	7.7	5	3.4	7	4.3	27	7.0
Cataplexy	37	7.7	8	5.4	3	1.8	29	7.5
Depression	37	7.7	8	5.4	11	6.7	25	6.4
Flu-like symptoms	37	7.7	6	4.1	2	1.2	31	8.0
Back pain	35	7.3	4	2.7	9	5.5	23	5.9
Pharyngitis	35	7.3	7	4.8	7	4.3	24	6.2
Anxiety	32	6.7	15	10.2	11	6.7	15	3.9
Cough	29	6.1	4	2.7	9	5.5	17	4.4
Myalgia	29	6.1	5	3.4	5	3.1	24	6.2
Diarrhea	28	5.9	6	4.1	12	7.4	15	3.9
Dizziness	26	5.4	7	4.8	7	4.3	16	4.1
Allergic reaction	25	5.2	6	4.1	3	1.8	17	4.4
Dry mouth	25	5.2	10	6.8	8	4.9	16	4.1
Somnolence	24	5.0	5	3.4	9	5.5	19	4.9

[a] Includes all patients who received at least one dose of modafinil.
[b] Includes all patients who reported the onset of an adverse event while receiving the indicated dose of modafinil. Patients could be counted more than once if they experienced a separate occurrence of the same adverse event while receiving different doses of modafinil (i.e. a new occurrence, after resolution of the prior occurrence, when switched to a different dose).

tooth disorder (12%), and nausea (11%). The majority of adverse events (95%) were rated as mild to moderate and transient in nature. The most common adverse events considered to be treatment related were headache (13%), nervousness (8%), and nausea (5%). Treatment-related cardiovascular adverse events were rare; the most common were palpitations (1.5%), hypertension (1.0%), and tachycardia (1.0%). There did not appear to be a direct relationship between the incidence rates of the most common adverse events of any cause or the most common treatment-related adverse events and the dose of modafinil taken at the time the adverse events occurred (Tables 3 and 4). Although the number of patients experiencing adverse events while receiving 400-mg doses of modafinil was considerably greater than the number of patients experiencing adverse events while receiving lower doses, it should be noted that for the large majority of patients, the duration of treatment with 400-mg doses was considerably longer than the duration of treatment with lower doses.

For the most part, the incidence rates of the most common adverse events (all cause and treatment related) did not appear to be substantially different between patients who had received placebo in the 9-week, double-blind trials and patients who had received modafinil in these trials. However, for patients who were previously naive to treatment with modafinil, there was a slight increase in the all-cause incidence of insomnia (8.1 vs. 2.5%), headache (46.3 vs. 40.9%), and dizziness (8.8 vs. 3.8%). For

Table 4
Incidence of treatment-related adverse events reported by ≥2.5% of patients[a]

Adverse event (AE)	All patients ($N = 478$)[b]		Dose of modafinil when the AE occurred[c]					
			200 mg ($N = 147$)		300 mg ($N = 163$)		400 mg ($N = 388$)	
	N	%	*N*	%	*N*	%	*N*	%
Headache	61	12.8	18	12.2	12	7.4	40	10.3
Nervousness	37	7.7	14	9.5	18	11.0	16	4.1
Nausea	24	5.0	7	4.8	6	3.7	13	3.4
Anxiety	21	4.4	10	6.8	7	4.3	9	2.3
Dry mouth	15	3.1	6	4.1	6	3.7	10	2.6
Somnolence	14	2.9	4	2.7	5	3.1	11	2.8
Cataplexy	13	2.7	5	3.4	1	0.6	10	2.6
Insomnia	13	2.7	6	4.1	2	1.2	6	1.5
Diarrhea	12	2.5	2	1.4	5	3.1	7	1.8

[a] Includes patients whose adverse event was considered possibly, probably, or definitely related to treatment by the investigator, but excludes adverse events considered remotely related or definitely unrelated.
[b] Includes all patients who received at least one dose of modafinil.
[c] Includes all patients who reported the onset of an adverse event while receiving the indicated dose of modafinil. Patients could be counted more than once if they experienced a separate occurrence of the same adverse event while receiving different doses of modafinil (i.e. a new occurrence after resolution of the prior occurrence, when switched to a different dose).

treatment-related adverse events, patients who were previously naive to modafinil treatment had a slight increase in the incidence of insomnia (5.6 vs. 1.3%) and nausea (6.9 vs. 4.1%).

A total of 137 patients (28.7%) discontinued treatment during the 40-week, open-label studies (Table 5). Fifty-five patients (11.5%) discontinued because of insufficient efficacy and 43 (9.0%) discontinued because of adverse events. The adverse events that resulted in discontinuation and that occurred more than once included nervousness ($N = 7$), nausea ($N = 4$), anxiety ($N = 3$), depression ($N = 3$), and infection ($N = 2$). The adverse events leading to discontinuation of treatment were identified for 37 of the 43 considered to be treatment related in 22 of these 37 patients (59%).

Table 5
Reasons for discontinuation of treatment

Reason for discontinuation	Number (%) of patients ($N = 478$)
Insufficient efficacy	55 (11.5)
Adverse event	43 (9.0)
Consent withdrawn	12 (2.5)
Noncompliance	12 (2.5)
Lost to follow-up	7 (1.5)
Other	8 (1.7)
Total	137 (28.7)

Twenty-three serious adverse events were reported during the two studies. Of these, three were considered to be possibly related to treatment – pyelonephritis ($N = 1$), dyspepsia ($N = 1$), and retinal hemorrhage ($N = 1$). The patient who experienced dyspepsia (rated as moderate in severity) discontinued treatment. Five patients experienced serious adverse events considered to be remotely related to treatment – chest pain ($N = 2$), palpitations ($N = 1$), cerebrovascular accident ($N = 1$), and carcinoma ($N = 1$). The patient who experienced the cerebrovascular accident discontinued treatment.

Overall, there were no clinically meaningful changes in vital signs, ECGs, or physical examinations during the 40-week, open-label studies. During the open-label studies, mean concentrations of gamma-glutamyl transferase (GGT) and alkaline phosphatase tended to increase slightly with time in a dose-dependent fashion. Twelve patients (2.5%) experienced clinically significant elevations in GGT levels (i.e. greater than three times the upper limit of normal) during the 40-weeks of open-label treatment; however, seven of these patients had elevated GGT levels at screening. Only one patient discontinued

treatment because of an abnormal GGT level. A clinically significant elevation of the level of aspartate aminotransferase ($N = 7$), alanine aminotransferase ($N = 6$), or total bilirubin ($N = 1$) was uncommon during the 40 weeks of open-label treatment.

4. Discussion

This is the first report of the long-term efficacy and safety of modafinil in a large cohort of patients with narcolepsy who were recruited from two 9-week, double-blind, placebo-controlled studies conducted in the United States. The study designs used in the long-term, open-label studies of modafinil for the treatment of EDS in narcolepsy followed two dosing practices commonly used in the clinical practice setting (i.e. flexible dose and optimized fixed dose), and employed the most common doses of modafinil used in the treatment of narcolepsy (i.e. 200, 300, and 400 mg).

As determined by physician-evaluated CGI-C scores, more than 80% of patients experienced an improvement in disease severity throughout the 40-week treatment periods, with approximately 10% experiencing no change in severity and approximately 10% experiencing a worsening of symptoms. After 2 weeks of open-label treatment, 49% of patients were rated as 'much improved' or 'very much improved'. After 8, 24, and 40 weeks of treatment, the percentage of patients rated as 'much improved' or 'very much improved' in the intention-to-treat population was significantly higher (58–59%) than at week 2. This may be due to the accrual of therapeutic benefits with longer treatment times or to the fact that dosage was optimized for most patients by the week 8 visit. Interestingly, a greater percentage of patients were receiving maintenance doses of 400 mg of modafinil (74–77%) at weeks 8, 24, and 40 than at week 2 (54%).

During the 2-week washout period before the start of open-label treatment with modafinil, mean ESS and QoL scores, which had improved significantly during double-blind treatment, returned to approximately the values observed at double-blind baseline. During the open-label studies, the mean ESS score improved significantly from 16.5 at baseline to a mean score of 12.2–12.9 and a median value of 12–13 at weeks 2 through 40. ESS scores of ≤ 10 are generally regarded as being within the normal range, although somewhat higher scores are observed in about 8–18% of otherwise normal populations (such as, students [21], the elderly [22], truck drivers [23], and 'sleepy workers' [24]). In contrast, ESS scores of ≥ 12 are reported by most patients with sleep disorders, including narcolepsy and idiopathic hypersomnia [16]. In the studies reported here, 75% of patients had moderate-to-severe narcolepsy, and half the patients reported near normal or normal scores on the ESS (i.e. ≤ 12) during treatment with modafinil.

QoL scores also were significantly improved over double-blind baseline scores for all SF-36 domains and metascales, with the exception of bodily pain and general health. The improvements in scores with modafinil treatment in the open-label studies are consistent with those reported for the 9-week, double-blind studies of modafinil [25] and are clinically significant. For instance, the 14- to 19-point improvement in the role function (physical) domain score observed with modafinil treatment during the 40-week study is consistent with the improvement observed in patients with migraine headaches who received treatment with sumatriptan [26]. The 13- to 15-point improvement in the vitality domain with modafinil treatment is similar to the improvement reported in patients with kidney failure who were treated with erythropoietin [27]. Finally, the 7- to 9-point improvement in the social functioning domain score demonstrated with modafinil treatment is comparable to the improvement observed in patients with chronic obstructive pulmonary disease who underwent a pulmonary rehabilitation program [28].

Adverse events were mostly mild to moderate in nature, and in general the incidence rates of adverse events did not appear to be related to the dose of modafinil taken or to prior treatment status (i.e. modafinil or placebo). Of the most commonly reported adverse events of all causes and the most common adverse events considered to be treatment related, headache, nausea, nervousness, and anxiety also were observed more frequently in patients receiving modafinil in the 9-week, double-blind trials than in patients receiving placebo [29]. Insomnia, also reported by more patients receiving modafinil than by those receiving placebo in the double-blind trials,

was reported by 4.4% of all patients in the open-label studies and was considered treatment related in 2.7% of patients. Nervousness, nausea, anxiety, and depression were the most common reasons for discontinuation of treatment because of adverse events in the open-label studies. Similarly, treatment discontinuation rates because of these adverse events were higher for patients receiving modafinil than for patients receiving placebo in the 9-week, double-blind trials [29].

During 40 weeks of open-label treatment, only 11.5% of patients discontinued modafinil therapy because of insufficient efficacy. This result suggests that the therapeutic response to modafinil is maintained in the majority of patients.

In the 9-week, fixed-dose, double-blind, placebo-controlled trials [11,12], there was no consistent evidence that dosages of 400 mg/day conferred additional therapeutic benefits beyond those observed with dosages of 200 mg/day; however, both dosages were generally well tolerated. In the open-label studies, the majority of patients (~75%) were assigned by the investigators to receive 400-mg doses of modafinil, and less than 20% of patients were maintained on the starting dose of 200 mg. This suggests that both the patients and the investigators preferred doses of 300 or 400 mg and confirms that these higher doses were well tolerated. The improvement in CGI-C scores reported at weeks 8 through 40 and the associated shift to higher maintenance doses of modafinil support this conclusion. Nonetheless, it should be noted that objective demonstration of dose-dependent improvements in efficacy remains to be demonstrated by additional, well-controlled, fixed-dose, clinical studies.

In summary, long-term (40-week) treatment with modafinil was effective in significantly reducing the symptoms of EDS associated with narcolepsy and improving the general QoL of patients with narcolepsy. Most patients were receiving daily doses of 400 mg of modafinil within 2 weeks of treatment and continued to receive this dose throughout 40 weeks of treatment. This dosing pattern, coupled with the rapid and sustained improvements in symptomatology reported with modafinil over the 40-week treatment period, suggests that efficacy is maintained and tolerance to modafinil does not develop in the majority of patients.

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