

Efficacy and Safety of Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Study

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ABSTRACT. *Objective.* Modafinil, which is structurally and pharmacologically different from other agents that are used for the treatment of children with attention-deficit/hyperactivity disorder (ADHD), selectively activates the cortex and has low potential for abuse. Initial studies of the use of modafinil to treat ADHD showed significant improvements in the core symptoms of the disorder, namely inattention, hyperactivity, and impulsivity. This study evaluated a new formulation of modafinil (modafinil film-coated tablets) in children and adolescents with ADHD.

Methods. This 9-week, multicenter, randomized, double-blind, placebo-controlled, flexible-dose study evaluated the film-coated tablet formulation of modafinil, which was titrated to an optimal dose on the basis of efficacy and tolerability (range: 170–425 mg once daily). Efficacy was assessed by clinicians who completed the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) based on interviews with teachers

(School Version) and parents (Home Version) and the Clinical Global Impression of Improvement scale. Safety evaluation was based on assessments of adverse event reports, laboratory tests, vital signs, and body weight.

Results. A total of 248 subjects were randomly assigned in a 2:1 ratio, and 246 were treated with modafinil ($n = 164$) or placebo ($n = 82$). Treatment groups were comparable with respect to demographics and baseline characteristics. Intention-to-treat analysis (ITT) showed that compared with placebo, treatment with modafinil significantly improved the core symptoms of ADHD as shown by greater reductions in the ADHD-RS-IV School Version total scores from baseline to final visit (mean change [SD]: -15.0 [11.8] vs -7.3 [9.7]) (effect size: 0.69; 95% confidence interval: 0.57–0.82). Significant improvements were observed with modafinil treatment on the ADHD-RS-IV School Version at week 1, with improvements maintained throughout the study. Similar differences in symptom improvements were observed on the ADHD-RS-IV Home Version between modafinil-treated and placebo-treated patients. Treatment with modafinil also significantly reduced subscale scores for inattention and hyperactivity-impulsivity on both School and Home Versions compared with placebo. At the final visit, 48% of modafinil-treated patients were rated as “much” or “very much” improved in overall clinical condition compared with 17% of placebo-treated patients (Clinical Global Impression of Improvement). Most adverse events were mild to moderate in severity, and the majority resolved during treatment. The most commonly reported adverse events in the modafinil group were insomnia (29%), headache (20%), and decreased appetite (16%). Three percent of modafinil-treated patients and 4% of placebo-treated patients discontinued treatment because of adverse events.

Conclusions. Modafinil film-coated tablets significantly improved ADHD symptoms at school and home as evaluated by clinicians, teachers, and parents. Treatment with once-daily modafinil was generally well tolerated, with few discontinuations as a result of adverse events. *Pediatrics* 2005;116:e777–e784. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0617; *modafinil, modafinil film-coated tablets, ADHD, efficacy, tolerability, clinical trial.*

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ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; CGI-S, Clinical Global Impression of Severity of Illness; ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; SBP, systolic blood pressure; DBP, diastolic blood pressure; CGI-I, Clinical Global Impression of Improvement; CPRS-R:S, Conners' Parent Rating Scale-Revised, Short Form; SSRS, Social Skills Rating System; CHQ, Child Health Questionnaire.

Attention-deficit/hyperactivity disorder (ADHD) is considered the most common neurobehavioral disorder of childhood and is estimated to affect 5% to 10% of school-aged children.^{1,2} Children with ADHD are at a higher risk for other psychiatric disorders, including disruptive behavior, mood, and anxiety disorders.³⁻⁶ Because of the adverse impact of ADHD on patients and caregivers, the disorder has been recognized as a public health concern.⁷

Although several pharmacotherapies for ADHD reduce symptoms, not all patients respond adequately, and the emergence of adverse events may limit their use in some patients.⁸⁻¹⁰ The Schedule II status of the central nervous system stimulants may also raise concerns regarding safety and longer term use.¹¹ Modafinil, which is structurally and pharmacologically different from other agents that are approved to treat ADHD, may improve symptoms of ADHD via the same mechanism by which it improves wakefulness. Preclinically, modafinil selectively activates the cortex without causing widespread central nervous system stimulation.¹²⁻¹⁴ Modafinil does not seem to activate areas of the brain that mediate reward and abuse and has a low potential for abuse.¹⁵

Treatment of children with ADHD with modafinil resulted in significant improvements in symptoms of the disorder in initial studies.¹⁶⁻¹⁹ Pharmacokinetic and pharmacodynamic modeling and clinical trial simulations were used to supplement the results from double-blind, dose-ranging studies of modafinil in children and adolescents to select dosages of 340 to 425 mg/day.¹⁷⁻²⁰ A concentrated form of modafinil was developed to produce a small tablet that would ease administration of these doses in the pediatric population.

This 9-week, randomized, double-blind, placebo-controlled, flexible-dosage trial evaluated the efficacy and the tolerability of this new formulation of modafinil for the treatment of children and adolescents with ADHD. On the basis of the results of the initial studies, we hypothesized that modafinil would be superior to placebo for the treatment of ADHD.

METHODS

Patients

Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*²¹ for ADHD at screening, as manifested by a psychiatric/clinical evaluation and the Diagnostic Interview Schedule for Children, Fourth Edition, with a Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher ("moderately ill" or worse).²² In addition, patients were attending full-time school (ie, they were not being home-schooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender,²³ were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children-Third Edition,²⁴ and had a score of at least 80 on the Wechsler Individual Achievement Test-Second Edition-Abbreviated.²⁵

Patients were excluded when they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or

other psychotic disorders (DSM-IV Axis I); evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; or other active clinically significant disease. To avoid potential ethical concerns, patients whose ADHD was well controlled and who were satisfied with current ADHD therapy (with low levels of side effects) were also excluded, as were those who had failed to respond to 2 or more adequate courses (dose and duration) of stimulant therapy for ADHD. Other exclusion criteria included a clinically significant drug sensitivity to stimulants, a history of alcohol or substance abuse as defined by DSM-IV criteria,²¹ consumption of >250 mg/day caffeine, absolute neutrophil count $<1 \times 10^9/L$, hypertension (systolic blood pressure [SBP] of ≥ 122 mm Hg or diastolic blood pressure [DBP] of ≥ 78 mm Hg for patients aged 6-9 years; SBP of ≥ 126 mm Hg or DBP of ≥ 82 mm Hg for patients aged 10-12 years; SBP of ≥ 136 mm Hg or DBP of ≥ 86 mm Hg for patients aged 13-17 years), hypotension (sitting SBP <50 mm Hg for patients younger than 12 years or <80 mm Hg for patients 12 years and older), and resting heart rate outside the range of 60 to 115 beats per minute. Concomitant use of prescription or nonprescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) and during the study.

The Institutional Review Board of each participating center reviewed and approved the study protocol. Written informed consent was obtained from the patient's parent or legal guardian before the study began, with assent obtained from the patient before enrollment, and all patients were free to withdraw from the study at any time. This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation's Good Clinical Practice Guidelines.

Study Design and Treatment

This randomized, double-blind, placebo-controlled, flexible-dose study was conducted at 24 sites in the United States from November 11, 2003, to June 11, 2004. A screening visit was conducted within 28 days of baseline testing to determine eligibility. Patients who satisfied all entry criteria and discontinued previous medication for ADHD over a 1- to 4-week washout period were randomly assigned 2:1 within each center to receive 9 weeks of treatment with modafinil film-coated tablets or matching placebo tablets once daily in the morning. The randomization code was generated by Cephalon, Inc (West Chester, PA) and implemented by a central agency (Phoenix Data Systems, Valley Forge, PA).

The dose of modafinil or placebo was individually titrated on the basis of tolerability and efficacy using the following schedule: 85 mg (1 tablet) on days 1 and 2, 170 mg (2 tablets) on days 3 to 7, 255 mg (3 tablets) on days 8 to 14, 340 mg (4 tablets) on days 15 to 21, and 425 mg (5 tablets) on day 22. Titration was stopped when any of the following conditions was met: poor tolerability, no additional expected incremental improvement in efficacy, patient's request, or achievement of a Clinical Global Impression of Improvement (CGI-I) rating of 1. The minimum and maximum daily dosages allowed during the study were 170 mg and 425 mg, respectively. Clinic visits were scheduled at baseline and weeks 1, 2, 3, 5, 7, and 9. Patients who completed at least 4 weeks of treatment and did not discontinue from the study because of an adverse event were eligible to participate in a 1-year, open-label extension study.

Efficacy Assessments

Efficacy was evaluated using the School and Home Versions of the ADHD-RS-IV, which assess the 18 symptoms in the DSM-IV diagnostic criteria for ADHD.²¹ Each item on the scale is scored from 0 to 3 (0 = never or rarely, 1 = sometimes, 2 = often, 3 = very often). The primary efficacy assessment was the change from baseline to final visit in total score on the ADHD-RS-IV School Version.²³ The subscale scores for inattention and hyperactivity-impulsivity for the ADHD-RS-IV School Version and the total, inattention, and hyperactivity-impulsivity scores on the Home Version were also evaluated.²³

Investigators completed the ADHD-RS-IV School Version, which was based on a semistructured interview with the patient's primary teacher before each visit at ~1:00 PM (± 1 hour). Investigators completed the ADHD-RS-IV Home Version at each visit, which was based on an interview with the patient's parent (and

the child, when appropriate) to assess perceptions of behavior during the evening hours (between 6:00 and 8:00 PM) and on weekends. When a patient withdrew from the study before the completion of the 9-week treatment phase, the last assessment completed was used as the final visit in the primary efficacy analysis.

Additional efficacy assessments included the CGI-I,²² Conners' Parent Rating Scale-Revised, Short Form (CPRS-R:S),²⁶ Social Skills Rating System (SSRS),²⁷ and Child Health Questionnaire (CHQ).²⁸ ADHD-RS-IV School and Home Version scores were assessed at baseline and weeks 1, 2, 3, 5, 7, and 9; the CGI-I at weeks 1, 2, 3, 5, 7, and 9; the CPRS-R:S and SSRS at baseline and weeks 3, 7, and 9; and the CHQ at baseline and week 9. All investigators (or qualified clinicians) received Internet-based training (ePharmaLearning, Conshohocken, PA) on the administration of these scales in an attempt to reduce variability in ratings across sites. Although all investigators completed this training course, they were not required to substantiate interrater reliability criteria before patients were evaluated. The same investigator was assigned to the same patient(s) whenever possible over the course of the study.

The CGI-S was used to evaluate the severity of the overall clinical condition associated with ADHD at baseline. At each visit, the investigator determined the change in the patient's overall clinical condition relative to baseline after discussion with the parent of the child's home behavior in the past week. All other parent-rated assessments were made within 24 hours of the scheduled visit, with each item rated according to the patient's behavior in the past week or since the last assessment.

Tolerability Assessments

Tolerability was evaluated by adverse events that were reported spontaneously by parents and patients at baseline and all study visits (weeks 1, 2, 3, 5, 7, and 9). Patients and parents were also instructed to report any adverse events at any time between study visits. The severity of each adverse event was rated as mild (no limitation of usual activities), moderate (some limitation of usual activities), or severe (inability to carry out usual activities). Vital signs and body weight were measured at baseline and weeks 1, 2, 3, 5, 7, and 9. Twelve-lead electrocardiograms and physical examinations were conducted at screening and week 9. Hematology testing was performed at baseline and weeks 1, 2, 3, 5, 7, and 9, and serum chemistry and urinalysis were performed at baseline and week 9.

Statistical Analyses

With the use of a 2-tailed *t* test at the .05 level of significance, ~150 patients (100 modafinil, 50 placebo) were needed to provide at least 90% power to detect a between-group difference of 6.03 units in the mean change from baseline in the primary efficacy assessment (ADHD-RS-IV School Version total score). This sample size was based on the assumption of variability in this assessment similar to that observed in a preliminary study of modafinil in ADHD (SD: 10.69).²⁹ To allow for study dropouts, a total enrollment of 180 patients was originally estimated to be required for this study. To ensure adequate patient exposure and to meet enrollment goals of this study, we undertook aggressive screening efforts. This resulted in an unexpected increase in the number of eligible patients who were available for participation in the study at screening. Although the protocol-specified enrollment was 180, eligible patients who were already in the screening phase of the study at the time when planned enrollment was reached were able to enroll also, thus increasing the number enrolled to 246. This primary efficacy analysis included patients who received at least 1 dose of study drug and had at least 1 postbaseline primary efficacy assessment. The safety analysis included patients who received at least 1 dose of study drug.

All statistical tests were 2-tailed, with a significance level of .05. Demographic and baseline characteristics were compared using an analysis of variance model with treatment and center as factors for continuous variables, Pearson's χ^2 test (or Fisher's exact test when cell sizes were <5) for nominal variables, or the Cochran-Mantel-Haenszel test adjusted for center for ordinal variables. Treatment group comparisons of all efficacy assessments, except CGI-I, were made using an analysis of covariance model, with treatment and center as factors and the corresponding baseline value as a covariate. CGI-I ratings were analyzed using the Coch-

ran-Mantel-Haenszel test adjusted for center. Treatment responders were defined as patients rated as much improved or very much improved on the CGI-I. Effect sizes were calculated for change in ADHD-RS-IV scores on the basis of the standardized mean difference as described by Hedges and Olkin.³⁰ To assess changes in body weight, we converted individual body weights to standardized *z* scores, which represent the number of SDs above or below the mean of the age- and gender-specific general pediatric and adolescent population.^{31,32}

RESULTS

Patients and Dosing

A total of 248 patients were randomly assigned into the study; 164 received modafinil film-coated tablets and 82 received placebo (2 patients who were randomly assigned to placebo were not treated; Fig 1). Fifty-two percent of patients completed the study. Discontinuation rates were higher in the placebo group (61%) than in the modafinil group (41%).

Demographics and baseline characteristics were similar between the 2 treatment groups (Table 1). At baseline, the overall mean age was 10.3 years, mean weight was 42.9 kg, and the majority (71%) of patients were male. Most (59%) patients had a combined ADHD subtype and were moderately or markedly ill (85%) as assessed by the CGI-S. In the modafinil group, the mean stable daily dose was 368.5 mg and the median was 425 mg.

Efficacy

Modafinil improved symptoms of ADHD as demonstrated by significant reductions in mean total scores on the ADHD-RS-IV School Version compared with placebo at the final visit (mean change [SD] from baseline: modafinil: -15.0 [11.8]; placebo: -7.3 [9.7]; *P* < .0001; Table 2, Fig 2). The effect size for ADHD-RS-IV School Version total score was 0.69 (95% CI: 0.57-0.82) at the final visit. Significant improvements were observed with modafinil treatment at week 1 (*P* = .020), with improvements maintained throughout the study (Fig 2). Statistically significant differences between treatment groups were also found on the ADHD-RS-IV School Version subscales; the modafinil-treated group had significantly greater reductions than those who received placebo in mean inattention (-8.8 [7.4] vs -5.0 [5.8]) and hyperactivity-impulsivity (-6.3 [6.4] vs -2.3 [5.6]) subscale scores at the final visit (*P* < .0001, for both; Table 2).

Results for the ratings on the ADHD-RS-IV Home Version were consistent with those for the ratings on the ADHD-RS-IV School Version (Table 2, Fig 3). Patients who were treated with modafinil demonstrated a significantly greater change from baseline in mean total score compared with placebo-treated patients at week 2 (*P* = .003) and all subsequent visits (final visit: modafinil: -14.3 [12.7]; placebo: -7.0 [10.1]; *P* < .0001; Fig 3). Effect size for the Home Version total score was 0.61 (95% CI: 0.48-0.73) at the final visit. Statistically significant between-group differences were also observed for the change in mean subscale scores for inattention (modafinil: -7.9 [7.1]; placebo: -3.8 [5.8]; *P* < .0001) and hyperactivity-impulsivity (modafinil: -6.4 [6.9]; placebo: -3.3 [5.6]; *P* = .001) at the final visit (Table 2).

Fig 1. Patient disposition. *Two patients who were randomly assigned to the placebo group did not receive study drug.

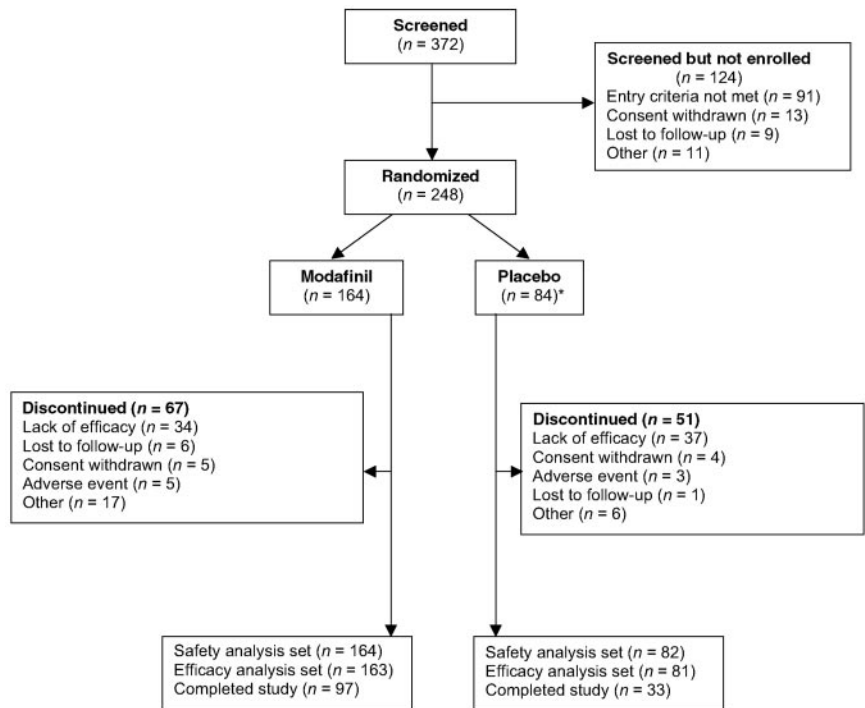


TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic*	Modafinil (n = 164)	Placebo (n = 82)
Age, y		
Mean (range)	10.4 (6–17)	10.1 (6–17)
Weight, kg		
Mean (range)	43.6 (20.2–85.4)	41.4 (18.6–82.1)
Gender, n (%)		
Male	113 (69)	61 (74)
Female	51 (31)	21 (26)
CGI-S score, n (%)		
Moderately ill	72 (44)	43 (52)
Markedly ill	66 (40)	27 (33)
Severely ill	25 (15)	12 (15)
Among the most extremely ill	1 (<1)	0
Current ADHD subtype, n (%)		
Inattentive	61 (37)	33 (40)
Hyperactive/impulsive	6 (4)	1 (1)
Combined	97 (59)	48 (59)
Previous ADHD treatment, n (%)†		
Methylphenidate/methylphenidate hydrochloride	56 (34)	27 (33)
Dexamphetamine sulfate	45 (27)	19 (23)
Atomoxetine hydrochloride	24 (15)	11 (13)
Other	10 (6)	2 (2)
No previous ADHD treatment, n (%)	88 (54)	45 (55)
Most frequently co-administered agents in >10% of patients, n (%)‡		
Non-opioid analgesics/anti-inflammatories	54 (33)	22 (27)
Respiratory agents	34 (21)	15 (18)
Anesthetics	24 (15)	17 (21)
Antihistamines	24 (15)	10 (12)
Other	62 (38)	33 (40)
ADHD-RS-IV total score, mean (SD)		
School Version	35.8 (9.2)	35.5 (8.9)
Home Version	37.7 (9.6)	36.9 (9.1)

* No statistically significant between-group differences were observed for any characteristic at baseline.

† Patients could have received >1 agent.

‡ Omitting vitamins/supplements.

Modafinil significantly improved patients' overall clinical condition as assessed by the CGI-I compared with placebo (Fig 4). A significantly greater proportion of patients who were treated with modafinil

than with placebo were classified as responders starting at week 2 ($P = .003$), with the benefit of modafinil sustained throughout the study. At the final visit, 48% of patients who were treated with

TABLE 2. Efficacy Outcomes Summary

Variable	Modafinil (n = 163)			Placebo (n = 81)			Δ	95% CI	P Value*
	Baseline	Final Visit	Change	Baseline	Final Visit	Change			
ADHD-RS-IV School Version									
Total score	35.7 (9.3)	20.7 (13.9)	-15.0 (11.8)	35.3 (8.8)	28.0 (12.7)	-7.3 (9.7)	-7.7	-10.8 to -4.9	<.0001
Inattention	21.1 (4.5)	12.3 (7.5)	-8.8 (7.4)	21.2 (4.1)	16.2 (6.7)	-5.0 (5.8)	-3.8	-5.7 to -2.1	<.0001
Hyperactivity-impulsivity	14.6 (8.0)	8.4 (7.9)	-6.3 (6.4)	14.1 (7.8)	11.7 (8.0)	-2.3 (5.6)	-4.0	-5.3 to -2.3	<.0001
ADHD-RS-IV Home Version									
Total score	37.8 (9.5)	23.6 (14.5)	-14.3 (12.7)	36.8 (9.1)	29.8 (12.1)	-7.0 (10.1)	-7.3	-9.9 to -3.6	<.0001
Inattention	21.8 (4.4)	13.9 (7.7)	-7.9 (7.1)	21.6 (4.3)	17.8 (6.6)	-3.8 (5.8)	-4.1	-5.7 to -2.1	<.0001
Hyperactivity-impulsivity	16.1 (7.6)	9.7 (8.1)	-6.4 (6.9)	15.2 (7.4)	11.9 (7.8)	-3.3 (5.6)	-3.1	-4.5 to -1.2	.001

CI indicates confidence interval; Δ, difference in change for modafinil versus placebo. Values represent means (SD); 95% CI of change from baseline for modafinil versus placebo.

* P value represents difference between modafinil and placebo in mean change from baseline to the final visit.

modafinil and 17% of placebo-treated patients were classified as responders ($P < .0001$).

On the CPRS-R:S domains of oppositional behavior, cognitive problems/inattention, hyperactivity, and ADHD index, patients who were treated with modafinil showed significantly greater improvement than patients who received placebo (all $P \leq .004$; Fig 5). At the final visit, modafinil also significantly improved some but not all aspects of the SSRS compared with placebo, including assertion, externalizing, hyperactivity, and problem behaviors total score (all $P \leq .022$), and the CHQ, including behavior, mental health, family activities, and psychosocial summary scores (all $P \leq .031$).

Tolerability

Modafinil was generally well tolerated. The most common adverse events in the modafinil group were insomnia, headache, and decreased appetite (Table 3). No patients discontinued from the study as a result of these adverse events. For the 48 (29%) patients who reported insomnia while receiving modafinil, 1 event was considered severe. When insomnia was reported, it occurred within 14 days of starting modafinil treatment in most patients (33 of 48, or 69%). In a majority (28 of 48, or 58%) of these patients, insomnia resolved while they continued active treatment. Twenty-six (16%) patients who re-

ceived modafinil reported decreased appetite; all events were considered mild or moderate in severity. In 16 (62%) of the 26 patients, decreased appetite was reported in the first 1 to 2 weeks of treatment. In a majority (19 of 26, or 73%) of the cases, appetite suppression resolved while they continued active treatment.

Almost all treatment-related adverse events were mild to moderate in severity. Three events were considered severe: insomnia and erythema multiforme, each in 1 patient who received modafinil, and headache in 1 patient who received placebo. Serious adverse events were reported for 2 patients in the modafinil group. Five days after discontinuing study medication, a 7-year-old boy received a diagnosis of Stevens-Johnson syndrome. Although the patient had an underlying viral syndrome, the investigator considered the event to be possibly related to study drug. An 8-year-old boy received a diagnosis of duodenitis, peptic ulcer, and hypertonia, all of which were reported by the investigator to be unrelated to study drug. Discontinuations as a result of adverse events were similar between treatment groups, occurring in 5 (3%) modafinil-treated patients and 3 (4%) patients in the placebo group. In addition to the 2 patients who discontinued modafinil as a result of serious adverse events (described above), 1 patient discontinued as a result of each of the following:

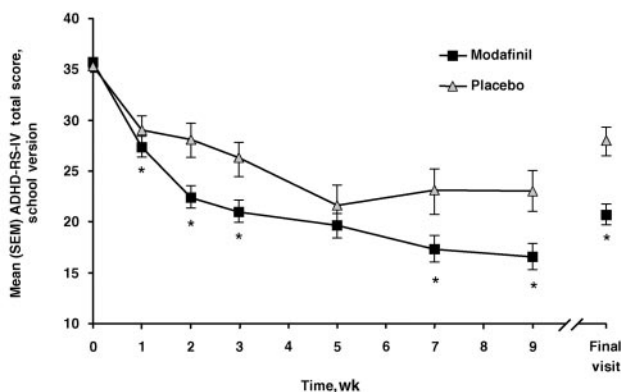


Fig 2. Teacher-/investigator-rated ADHD-RS-IV School Version: mean (standard error of mean) total score by visit. *Significant difference between modafinil film-coated tablets and placebo in mean change from baseline; $P = .020$ at week 1, $.0005$ at week 2, $.001$ at week 3, $.042$ at week 7, $.016$ at week 9, and $<.0001$ at the final visit.

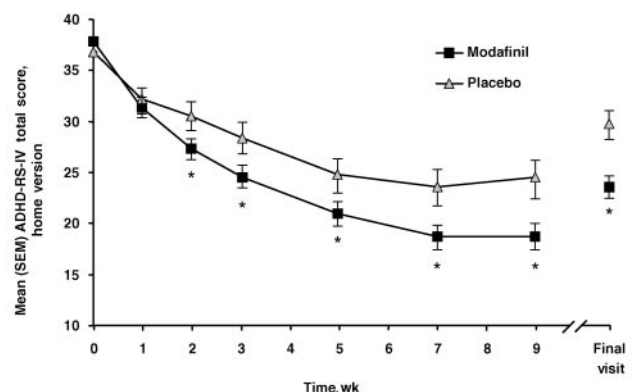


Fig 3. Parent-/investigator-rated ADHD-RS-IV Home Version: mean (standard error of mean) total score by visit. *Significant difference between modafinil film-coated tablets and placebo in mean change from baseline; $P = .003$ at week 2, $.001$ at week 3, $.008$ at week 5, $.012$ at week 7, $.009$ at week 9, and $<.0001$ at the final visit.

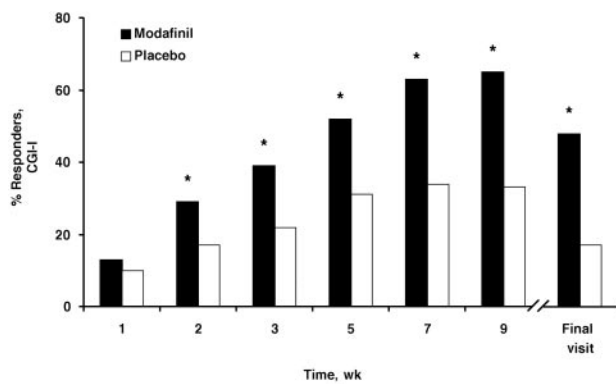


Fig 4. Percentage of responders on the CGI-I scale. *Significant difference between modafinil film-coated tablets and placebo; $P = .003$ at week 2, $.007$ at week 3, $.027$ at week 5, $.015$ at week 7, $.037$ at week 9, and $<.0001$ at the final visit.

somnolence, dystonia, and tachycardia. One patient in the placebo group discontinued as a result of nervousness and emotional lability and 1 each as a result of hostility and hyperkinesia.

There were no clinically significant changes in mean heart rate, blood pressure (Table 4), or 12-lead electrocardiogram results. Weight changes were small but in opposite directions for the placebo group (a mean increase of 0.8 kg; a z score change, mean of 0.05) and the modafinil group (a mean decrease of 0.8 kg; a z score change, mean of -0.17), and the between-group difference was statistically significant ($P < .0001$, for both weight change and z score change). However, no patient in either treatment group showed a clinically meaningful change in body weight when individual weights were corrected for age- and gender-specific means for the general pediatric and adolescent population. There were no clinically meaningful changes from baseline in mean laboratory evaluations.

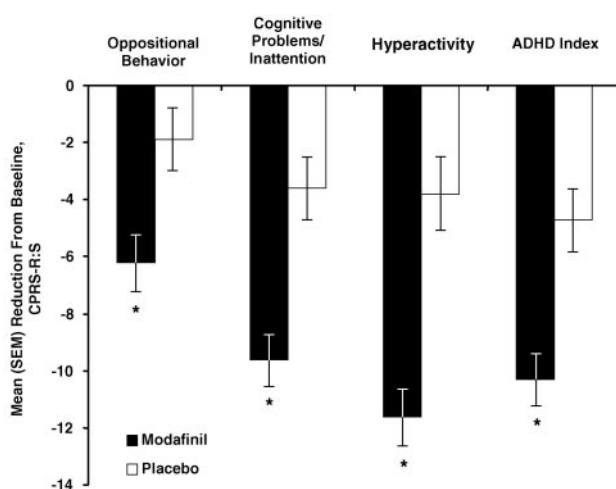


Fig 5. CPRS-R:S: mean (standard error of mean) changes from baseline to the final visit. *Significant difference between modafinil film-coated tablets and placebo in mean change from baseline; $P = .004$ (95% confidence interval [CI]: -7.1 to -1.3) for oppositional behavior, $<.0001$ (95% CI: -8.6 to -3.1) for cognitive problems/inattention, $<.0001$ (95% CI: -10.4 to -3.9) for hyperactivity, and $.0001$ (95% CI: -8.3 to -2.6) for ADHD index.

TABLE 3. Adverse Events Reported in at Least 5% of Patients in Either Treatment Group

Adverse Event	Modafinil (n = 164)	Placebo (n = 82)
Insomnia*	48 (29)	3 (4)
Headache	32 (20)	12 (15)
Decreased appetite*	26 (16)	3 (4)
Infection	19 (12)	12 (15)
Rhinitis	16 (10)	9 (11)
Pharyngitis	14 (9)	5 (6)
Cough increased	13 (8)	7 (9)
Abdominal pain	12 (7)	9 (11)
Rash	10 (6)	3 (4)
Vomiting	10 (6)	7 (9)
Accidental injury	8 (5)	5 (6)
Nervousness	7 (4)	5 (6)
Fever	8 (5)	2 (2)
Pain	8 (5)	1 (1)
Asthenia	6 (4)	4 (5)
Somnolence	4 (2)	4 (5)

Values represent number (%) of patients.

* $P < .05$ for modafinil versus placebo.

DISCUSSION

In this 9-week, double-blind study, treatment with modafinil film-coated tablets significantly improved the symptoms of ADHD compared with placebo on the ADHD-RS-IV School and Home Versions. Patients who received modafinil demonstrated significant improvements over placebo on total and subscale scores of both versions of the ADHD-RS-IV as rated by investigators on the basis of interviews with teachers and parents. The effect size for the primary assessment was 0.69, which is considered moderate to large in magnitude. These data indicate that once-daily modafinil was effective on the core symptoms of ADHD, namely inattention, hyperactivity, and impulsivity, both at school and at home. Patients' overall clinical condition, as assessed by the CGI-I, also significantly improved with modafinil treatment. These significant treatment effects were consistently observed within 1 to 2 weeks of initiating treatment and were maintained with continued therapy.

Parental assessments on all domains of the CPRS-R:S (ADHD, hyperactivity, cognitive problems/inattention, and oppositional behavior) showed significant improvements in ADHD symptoms and negative behaviors as a result of modafinil treatment. In addition, patients who received modafinil had significant improvements in some aspects of the SSRS (assertion, externalizing, hyperactivity, and problem behaviors total score) and the CHQ (behavior, mental health, family activities, and psychosocial summary scores) compared with those who received placebo.

Modafinil was generally well tolerated in this patient population. Adverse events were generally mild to moderate in severity, and discontinuations as a result of adverse events were similar for the modafinil and placebo groups. Among the most common adverse events, insomnia and decreased appetite were reported significantly more often in patients who received modafinil than in those who received placebo. Insomnia was mild or moderate in nearly all cases and did not result in discontinuation from the study. There were no statistically significant

TABLE 4. Vital Signs

Variable	Modafinil (n = 164)		Placebo (n = 82)		P Value
	Baseline	Final Visit	Baseline	Final Visit	
Heart rate, bpm	82.0 (11.1)	82.8 (11.6)	83.1 (11.1)	84.9 (11.3)	.228
SBP, mm Hg	106.4 (10.3)	105.5 (10.5)	105.3 (10.1)	104.3 (11.2)	.763
DBP, mm Hg	64.4 (7.8)	64.0 (8.1)	63.8 (7.4)	64.4 (8.4)	.349

bpm indicates beats per minute. Values represent means (SD).

differences or clinically meaningful changes in heart rate or blood pressure with modafinil treatment compared with placebo. Patients who were treated with modafinil had modest but statistically significant weight loss compared with those who received placebo. The magnitude of change was relatively small when individual patients' weights were compared with age- and gender-specific norms.

These results need to be viewed in light of some methodologic limitations. Patients whose ADHD did not respond to 2 or more previous ADHD medications were not included in the study, which may have excluded some treatment-resistant patients. Patients who were well treated with stimulants were not included in the study, which may have excluded some patients who also would have responded well to modafinil. Patients had the option to switch to open-label treatment after week 4 but before the end of the study. Although this provision was included to protect symptomatic patients from receiving placebo for a prolonged period, it may have contributed to an increase in discontinuations, particularly in the placebo group. This increase in discontinuations may have led to lowering of the mean total score on the ADHD-RS-IV (School Version) in the placebo group at week 5 by not counting patients who discontinued as a result of lack of efficacy at week 5, resulting in lack of a statistical difference versus the modafinil group. Because the study was only 9 weeks long, it is unknown whether the initial benefits will be sustained over longer periods of time. Additional studies are needed to determine the longer term efficacy and safety of modafinil in children and adolescents with ADHD.

Despite these considerations, this 9-week, double-blind, controlled study of patients who were randomly assigned to treatment with modafinil or placebo provides evidence that modafinil film-coated tablets that are administered once daily improve the full spectrum of symptoms of ADHD, including inattention, impulsivity, and hyperactivity, in children and adolescents. Benefits of modafinil were evident at school and at home. Significant improvements in ADHD symptoms occurred by the first week of treatment and were maintained throughout the 9-week study. Modafinil was generally well tolerated, with a low rate of discontinuations as a result of adverse events. The efficacy and safety profile of modafinil film-coated tablets, as well as its low potential for abuse, may offer clinicians and parents a new pharmacologic treatment option for children and adolescents with ADHD.

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Efficacy and Safety of Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Study

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