Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study Followed by Abrupt Discontinuation

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Objective: The objective of this fixed-dose study was to determine the efficacy and safety of a new formulation of modafinil (modafinil film-coated tablets) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). In addition, the effect of abrupt discontinuation of modafinil was evaluated in a 2-week observation period.

Method: Patients aged 6 to 17 years with DSM-IV-TR–defined ADHD were randomly assigned to 7 weeks of double-blind treatment with modafinil or placebo in a 2:1 ratio, followed by abrupt discontinuation of modafinil and a 2-week, double-blind observation period in which 46% of patients receiving modafinil were switched to placebo without tapering and half continued to receive modafinil. Study drug was administered once daily and titrated over the first 7 to 9 days to daily doses of 340 mg for patients < 30 kg or 425 mg for patients ≥ 30 kg. Assessment instruments included the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School and Home Versions and Clinical Global Impressions-Improvement scale (CGI-I). The study was conducted from November 2003 to June 2004.

Results: A total of 190 patients were randomly assigned to receive modafinil (340 mg, N = 44; 425 mg, N = 82) or placebo (N = 64). 189 patients were evaluated for safety. Modafinil significantly improved symptoms of ADHD as shown by reductions in ADHD-RS-IV School Version total scores compared with placebo at all visits ($p \leq .009$), including the final visit of the double-blind phase ($p < .0001$). With modafinil, ADHD-RS-IV School Version mean total scores changed from 37.8 at baseline to 29.3 at week 1 and 20.7 at final visit; corresponding placebo values were 36.6, 32.8, and 28.4, respectively; effect size at final visit was 0.76 (95% CI = 0.63 to 0.88). Total scores on the ADHD-RS-IV Home Version were also significantly reduced at all visits ($p \leq .022$) and final visit ($p = .001$) in patients receiving modafinil compared with those receiving placebo. Significantly higher proportions of patients receiving modafinil were rated "much improved" or "very much improved" in overall clinical condition (CGI-I) at all visits compared with patients receiving placebo ($p < .001$). No withdrawal symptoms were observed when modafinil was abruptly discontinued at the beginning of the final 2-week observation period. Modafinil was generally well tolerated. Insomnia, headache, and decreased appetite were the most commonly reported adverse events. Sixty-three percent of patients who received modafinil completed the study; 13% discontinued because of lack of efficacy; 10%, because of adverse events; and 13%, for other reasons (e.g., consent withdrawn, lost to follow-up).

Conclusion: Modafinil significantly improved symptoms of ADHD both at school and at home and was well tolerated by children and adolescents. Abrupt discontinuation of modafinil was not associated with symptoms of withdrawal or with rebound of symptoms of ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in the pediatric population, with an estimated prevalence of about 5% among school-aged children.[1] Characterized by inattention, hyperactivity, and impulsivity, ADHD has widespread manifestations that lead to problems both at school and at home. Approved treatments for ADHD include central nervous system (CNS) stimulants (methylphenidate and amphetamine), with effects that include the inhibition of reuptake of dopamine, and atomoxetine, a norepinephrine reuptake inhibitor. However, not all patients respond to these agents, some patients experience treatment-limiting adverse events (e.g., nervousness, agitation, cardiovascular effects, or gastrointestinal symptoms), and concerns about the abuse potential of stimulants may limit their use.[2–6]

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Modafinil is structurally and pharmacologically different from the CNS stimulants and may reduce the symptoms of ADHD via the same mechanism by which it improves wakefulness—selective activation of the cortex without generalized effects on the CNS, as shown in animal studies.[7–9] Modafinil does not appear to activate those areas of the brain involved in mediating reward and has a low potential for abuse.[10–12] Initial studies conducted in children with ADHD showed significant improvements in symptoms of the disorder with modafinil[13–16] and suggested that a higher dose of modafinil may be needed in children and adolescents than that used for the treatment of narcolepsy in adults.[17,18] Pharmacokinetic and pharmacodynamic modeling[19] and clinical study simulations[16] were used to supplement the results from double-blind, dose-ranging studies of modafinil in children and adolescents[14,15] to select for evaluation weight-dependent dosages of 340 and 425 mg/day of a new formulation of modafinil, modafinil film-coated tablets, which have a higher active ingredient–to-excipient ratio.

We hypothesized that modafinil would be effective and well tolerated for the treatment of ADHD and would not result in symptoms of withdrawal or rebound of symptoms of ADHD when abruptly discontinued. This 7-week, randomized, double-blind, placebo-controlled study assessed the efficacy and tolerability of modafinil in children and adolescents with ADHD. Following abrupt discontinuation of modafinil, patients were monitored over a 2-week, double-blind, observation period to evaluate symptoms of withdrawal or rebound of symptoms of ADHD.

METHOD

Patients

Male or female patients aged 6 to 17 years who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[20] criteria for ADHD were eligible for enrollment. Additional inclusion criteria included a Clinical Global Impressions-Severity of Illness scale (CGI-S)[21] rating of 4 or higher ("moderately ill" or worse), total and/or subscale scores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version[22] at least 1.5 standard deviations above norms for the patient's age and gender, an intelligence quotient of at least 80 as estimated by the Wechsler Intelligence Scale for Children-Third Edition,[23] and a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated.[24] Patients were eligible if they were attending a full-time school (i.e., they were not eligible if receiving home schooling) and if a teacher and parent (or legal guardian) were willing and able to participate for the duration of the study.

Patients with a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV-TR Axis I) were excluded from the study, as were those with a clinical assessment of current suicide risk or other psychiatric comorbidities requiring pharmacotherapy. To avoid potential ethical concerns, patients whose symptoms were very well controlled and who were satisfied with current therapy for ADHD (with low levels of adverse events) were also excluded, as were those who had failed to respond to 2 or more adequate courses of stimulant therapy for ADHD with trials on a range of doses and immediate- and controlled-release formulations. Patients were excluded if their height or weight was below the 5th or above the 95th percentile based on National Center for Health Statistics growth charts.[25]

Additional exclusion criteria were hypertension (defined as systolic blood pressure [SBP] ≥ 122 mm Hg or diastolic blood pressure [DBP] ≥ 78 mm Hg for children aged 6–9 years; ≥ 126 mm Hg or ≥ 82 mm Hg, respectively, for ages 10–12; and ≥ 136 mm Hg or ≥ 86 mm Hg, respectively, for ages 13–17), hypotension (defined as sitting SBP < 50 mm Hg for children < 12 years of age or < 80 mm Hg for children ≥ 12 years of age), resting heart rate outside the range of 60 to 115 beats per minute, absolute neutrophil count below 1×10^9/L, history of alcohol or substance abuse, and habitual consumption of more than 250 mg/day of caffeine. Patients were not allowed to use prescription or nonprescription medications with psychotropic activity, including other treatments for ADHD and dietary supplements, within 1 week of baseline (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) or throughout the study.

Prior to enrollment, written informed consent was obtained from the parent, with assent obtained from the patient. The institutional review board of each participating center reviewed and accepted the protocol. The study was conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation.

Study Design

This was a 7-week, multicenter, randomized, fixed-dose, double-blind, placebo-controlled study of modafinil film-coated tablets (340 or 425 mg/day depending on weight). At the end of 7 weeks, a 2-week observation period followed abrupt discontinuation of modafinil. Seventeen U.S. centers participated in the study, which was conducted from November 2003 to June 2004. Before baseline testing, prior medication for ADHD was washed out over a 1- to 4-week period. At the end of the baseline visit, patients were randomly assigned within strata defined by weight (< 30 or ≥ 30 kg) in a 2:1 ratio to receive once-daily modafinil or placebo in the morning. Patients weighing < 30 kg received modafinil (Cephalon, Inc.; Frazer,

Pa.) 340 mg or matching placebo, and those weighing ≥ 30 kg received modafinil tablets 425 mg or matching placebo. Modafinil was titrated during the first 7 to 9 days of the study according to the following schedule: 85 mg (1 tablet) on day 1, with the dose increased by 85 mg every other day until the predetermined dose was reached. Therefore, the administered doses were 85 mg (days 1 and 2), 170 mg (days 3 and 4), 255 mg (days 5 and 6), 340 mg (days 7 and 8 and thereafter for the < 30 kg stratum), and 425 mg (day 9 and thereafter for the ≥ 30 kg stratum). Each patient remained at his or her randomized dose through week 7. For the final 2 weeks, patients receiving modafinil either continued to receive modafinil at the dose they had been receiving or were switched to placebo in a randomized, double-blind manner. Patients already receiving placebo continued to receive placebo. This double-blinded approach of abrupt discontinuation followed by a 2-week observation period was used to evaluate the occurrence of symptoms of withdrawal or rebound of symptoms of ADHD.

Assessments

Following baseline evaluations, patients were scheduled to return to the clinic at weeks 1, 2, 3, 5, 7 (last visit), and 9 (last 2-week observation period visit). Patients who completed at least 4 weeks of the study (and did not discontinue because of an adverse event) could elect to participate in a 1-year open-label extension study.

Efficacy assessments. The primary outcome measure was the ADHD-RS-IV, an instrument used to assess the 18 symptoms of ADHD as defined in the DSM-IV-TR[20] using a 4-point Likert scale (0 = never or rarely, 1 = sometimes, 2 = often, 3 = very often). The primary efficacy measure was the mean change in total score from baseline to last visit on the teacher-/investigator-rated ADHD-RS-IV School Version.[22] Additional efficacy measures included change from baseline to each visit in the total, inattention, and hyperactivity-impulsivity scores on the ADHD-RS-IV School Version and the parent-/investigator-rated ADHD-RS-IV Home Version.[22]

Teachers completed the questionnaire following observation of their students at the same time of day (1:00 p.m. ± 1 hour) throughout the study. Their ratings were then reported to the site investigator at a predesignated time later that day. Investigators then completed the ADHD-RS-IV School Version based on this interview with the teacher. The ADHD-RS-IV Home Version was completed by the investigator at each visit based on an interview with the patient's parent (and the child, when appropriate) to assess the symptomatic frequency that best described the child's behavior at home (in accordance with DSM-IV-TR) since the last visit. If a patient withdrew from the study before 7 weeks, the last assessment completed was used as the final visit in the primary efficacy analysis.

Secondary efficacy assessment instruments also included the Clinical Global Impressions-Improvement scale (CGI-I)[21]; Test of Variables of Attention (TOVA)[26,27]; Conners' Parent Rating Scale-Revised, Short Form (CPRS:R-S)[28]; Social Skills Rating Scale (SSRS)[29]; and Child Health Questionnaire (CHQ).[30] To reduce the variability in ratings across sites, all investigators (or qualified clinicians) received standardized Internet-based training on the administration of these scales (ePharma Learning, Conshohocken, Pa.). Although all investigators completed this course, they were not required to fulfill any interrater reliability criteria before evaluating patients. To maintain consistency across efficacy assessments, the same investigator evaluated the same child at all clinic visits.

The severity of the patient's overall clinical condition at baseline was evaluated using the CGI-S. At each visit, the investigator determined the change in the patient's overall clinical condition (using the CGI-I) over the past week relative to baseline following discussion with the parent of the child's behavior at home.

At baseline and clinic visits at weeks 3 and 7, patients completed the TOVA, an objective test sometimes used in the assessment of ADHD. The parent completed the CPRS:R-S and SSRS at baseline visit and within 24 hours of scheduled visits at weeks 3 and 7, with items rated according to the patient's behavior since the last assessment (CPRS:R-S) or over the past week (SSRS). At week 9, the ADHD-RS-IV School and Home Versions and CGI-I were administered to evaluate the effect of abrupt discontinuation of modafinil on symptoms of ADHD. The CHQ was administered at baseline and weeks 7 and 9.

Tolerability assessments. Tolerability was evaluated by collection of adverse event reports from parents and patients at baseline and all study visits (weeks 1, 2, 3, 5, 7, and 9) as well as at any time between these visits. The severity of each adverse event was classified as "mild," "moderate," or "severe" according to the degree of limitation of usual activity associated with the event. Physical examinations were conducted at screening and week 7. At each clinic visit, vital signs, body weight, and hematologic parameters were evaluated; serum chemistry, urinalysis, and an electrocardiogram (ECG) were evaluated at baseline and weeks 7 and 9. At baseline and weeks 8 and 9, investigators conducted interviews (via telephone at week 8) with parents of patients to complete the Subject's Treatment Emergent Symptom Scale (STESS),[21] a 32-item scale used to assess the possible presence and degree of physical and emotional complaints of the patient during the 2-week observation period.

Statistical Analysis

Using a 2-tailed t test at the .05 level of significance, a sample size of approximately 150 patients (randomly assigned according to a 2:1 ratio as independent groups of

100 to modafinil and 50 to placebo) would provide at least 90% power to detect a between-group difference of 6.03 in the mean change from baseline in the ADHD-RS-IV School Version total score. This sample size was based on an estimated standard deviation of 10.69 as observed in a previous study of modafinil in children and adolescents with ADHD.[31] This primary efficacy analysis used the "last-observation-carried-forward" procedure and thus included patients who received at least 1 dose of the study drug and had at least 1 postbaseline assessment on the primary efficacy outcome measure. The safety analysis included patients who received at least 1 dose of the 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, stratum (body weight < 30 kg or ≥ 30 kg), and treatment-by-stratum interaction as factors for continuous variables; Pearson χ^2 test (or Fisher exact test if cell sizes were below 5) for nominal variables; or the Cochran-Mantel-Haenszel test adjusted for strata for ordinal variables. For each efficacy outcome measure (except the CGI-I ratings and TOVA), mean change from baseline to each visit through week 7 was compared between groups using an analysis of covariance (ANCOVA) model, with treatment, stratum, and treatment-by-stratum interaction as factors and the baseline value as a covariate. Effect size was calculated for change in ADHD-RS-IV School Version scores based on the standardized mean difference as described by Hedges and Olkin.[32] CGI-I ratings were analyzed using the Cochran-Mantel-Haenszel test adjusted for strata. Responders were defined as patients rated as "much improved" or "very much improved" on the CGI-I. TOVA ADHD scores were analyzed using the ANCOVA model after rank transformation. All efficacy variables at week 9 were summarized using descriptive statistics.

To assess changes in body weight, individual body weights were converted to standardized z scores, which represent the number of standard deviations above or below the mean age- and gender-specific data for the general pediatric and adolescent population.[33,34] A clinically meaningful change was defined as a decrease or increase of 1 in z score (i.e., 1 standard deviation [SD]) and an absolute value greater than 1.5 (i.e., below the 15th percentile for decrease and above the 85th percentile for increase in a normally distributed variable).

RESULTS

Patients

A total of 190 patients were randomly assigned to receive modafinil (N = 126) or placebo (N = 64) within weight strata, and 189 patients were evaluable for safety (Figure 1). Forty-four patients with a mean (SD) age of 7.5 (1.4) years and mean (SD) body weight at baseline of 25.2 (2.9) kg received modafinil 340 mg, 81 patients with mean age of 11.6 (2.6) years and mean weight of 48.8 (15.3) kg received modafinil 425 mg, and 64 patients with mean age of 9.7 (3.1) years and mean weight of 39.9 (18.4) kg received placebo. Sixty-three percent of patients completed the double-blind period (64.0% in the modafinil group and 62.5% in the placebo group; Figure 1).

Demographics and baseline clinical characteristics were similar between the modafinil and placebo groups (Table 1). Patients had a mean age of 10 years, and the majority were male (71%) and white (80%).

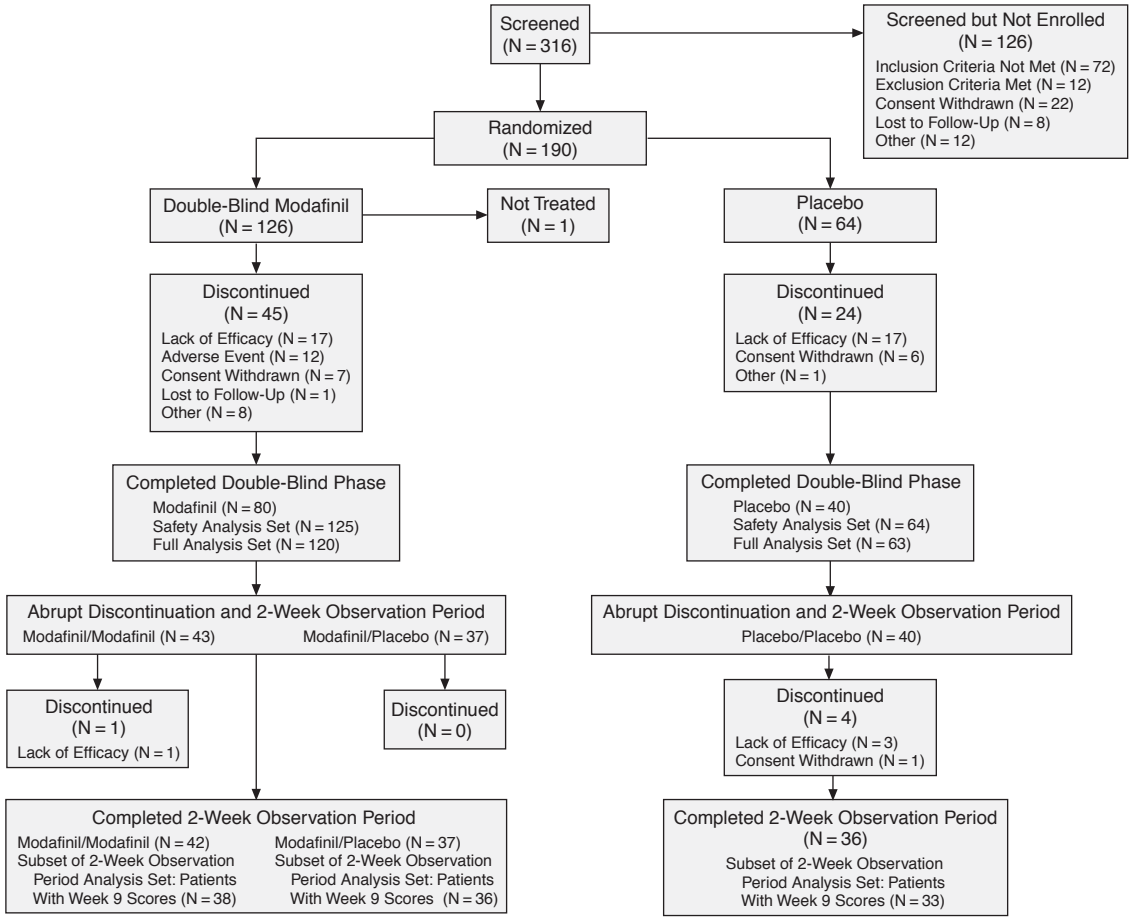
Double-Blind Phase (baseline to week 7)

Modafinil significantly improved symptoms of ADHD across multiple assessments compared with placebo, with similar results observed for children weighing < 30 kg and those weighing ≥ 30 kg. Modafinil significantly reduced total scores on the ADHD-RS-IV School Version ratings (of behavior at 1:00 p.m.) at week 1 compared with placebo ($p = .009$), with continued, significant improvement at all subsequent visits ($p \leq .006$) (Figure 2). The mean (SD) change from baseline to final visit was –17.2 (12.8) for modafinil versus –8.2 (10.3) for placebo ($p < .0001$) (Table 2). Between-group differences for the School Version subscale scores for inattention ($p = .0004$) and hyperactivity-impulsivity ($p < .0001$) were also significant for modafinil versus placebo at the final visit. The effect size for ADHD-RS-IV School Version total score was 0.76 (95% CI = 0.63 to 0.88) at the final visit.

Changes in the ratings on the ADHD-RS-IV Home Version (of child's behavior at home) were similar to those on the School Version; compared with placebo, modafinil significantly reduced mean total scores at all visits (Figure 3). The mean change from baseline to final visit for modafinil compared with placebo was –13.8 (14.3) versus –7.6 (13.0), respectively ($p = .001$) (Table 2). Subscale scores for inattention and hyperactivity-impulsivity were also significantly reduced in patients receiving modafinil compared with those receiving placebo ($p = .0007$ and $p = .004$, respectively) (Table 2).

The proportion of patients rated by the investigators as "much improved" or "very much improved" on the CGI-I assessment of overall clinical condition was significantly greater in the modafinil group than in the placebo group starting at week 1 ($p < .001$), and this differential effect was larger throughout the 7-week double-blind phase (Figure 4). At the final visit of the double-blind phase, 37% of patients receiving modafinil and 17% of patients receiving placebo were classified as "much improved" or "very much improved" using the CGI-I ($p < .001$). If patients with ratings of "minimally improved" according to the CGI-I assessment were also included, the proportion of patients receiving modafinil with any improvement increased to 65% compared with 35% for those receiving

Figure 1. Patient Disposition



placebo. At final visit, the percentage of patients with "no change" who received modafinil was 24% compared with 54% for those who received placebo. Corresponding values for modafinil compared with placebo for "minimally worse" were 6% and 8% and "much worse," 4% and 3%, respectively. One patient who received modafinil and no patients who received placebo were "very much worse."

On the CPRS:R-S, significant improvements ($p < .001$) with modafinil were observed for the ADHD index and total cognitive problems/inattention and hyperactivity subscale scores (Table 2). Significantly different changes from baseline in the mean TOVA ADHD score for modafinil compared with placebo were observed due to greater deterioration in the placebo group and relative stability in the modafinil group. The decrease observed in the modafinil group (mean score at final visit, –3.7; change from baseline, –0.5) was less pronounced than in the placebo group (–4.5 and –0.7, respectively), and the between-group difference was significant at the end of the double-blind phase ($p = .046$). On the SSRS and the CHQ, significant effects of modafinil were present in some, but not all, measures; for example, the problem behaviors total score ($p = .031$) and CHQ psychosocial summary score ($p = .039$).

Abrupt Discontinuation and 2-Week Observation Period (weeks 8 and 9)

The 2-week, double-blind observation period after abrupt discontinuation of modafinil did not reveal the presence of symptoms of withdrawal or rebound of symptoms of ADHD. Mean (SD) reductions in STESS scores were comparable between patients who abruptly discontinued modafinil and those who continued modafinil (–5.5 [8.3] vs. –4.0 [9.2]), indicating that abrupt discontinuation of modafinil did not adversely affect physical or emotional health. This design also allowed for the double-blind evaluation of the degree to which symptoms of ADHD returned to baseline levels for patients switched to placebo during the 2-week period; total scores on the ADHD-RS-IV School Version did not return to baseline levels and were comparable to the scores for patients who continued with modafinil therapy ($p > .05$). Compari-

Table 1. Demographic and Baseline Characteristics of Children and Adolescents With ADHD

Characteristic[a]	Modafinil (N = 125)	Placebo (N = 64)
Age, mean (range), y	10.1 (6–17)	9.7 (6–17)
Weight, mean (range), kg	40.5 (19.6–98.4)	39.9 (20.1–91.2)
Gender, N (%)		
Male	93 (74)	42 (66)
Female	32 (26)	22 (34)
CGI-S score, N (%)		
Moderately ill	79 (63)	38 (59)
Markedly ill	32 (26)	23 (36)
Severely ill	14 (11)	3 (5)
Current ADHD subtype, N (%)		
Inattentive	35 (28)	16 (25)
Hyperactive/impulsive	5 (4)	5 (8)
Combined	84 (67)	42 (66)
Previous ADHD treatment, N (%)[b]		
Total	66 (53)	38 (59)
Methylphenidate hydrochloride	43 (34)	26 (41)
Amphetamine salts	40 (32)	18 (28)
Atomoxetine hydrochloride	22 (18)	13 (20)
Other	6 (5)	6 (9)
Patients receiving coadministered agents, N (%)[b]	45 (36)	24 (38)
Respiratory agents	13 (10)	7 (11)
Vitamins/nutritional supplements	4 (3)	1 (2)
Nonopioid analgesics/ anti-inflammatories	24 (19)	15 (23)
Antihistamines	9 (7)	2 (3)
Anti-infectives	9 (7)	3 (5)
Other	17 (14)	5 (8)
ADHD-RS-IV total score, mean (SD)		
School Version	37.7 (9.1)	36.8 (9.3)
Home Version	38.8 (9.0)	38.8 (10.6)

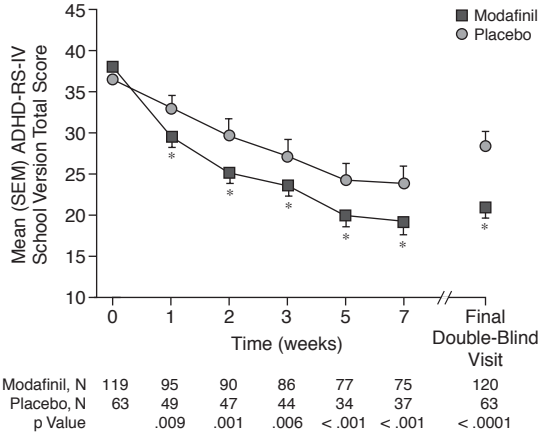
[a]No statistically significant between-group differences were observed for any characteristic at baseline.
[b]Patients could have received more than 1 agent.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV Home Version = parent-/investigator-rated ADHD Rating Scale-IV, ADHD-RS-IV School Version = teacher-/investigator-rated ADHD Rating Scale-IV, CGI-S = Clinical Global Impressions-Severity of Illness scale.

sons of the 3 groups of this period showed that both modafinil groups (continuation and discontinuation) experienced greater overall improvements compared with placebo (mean change from baseline to last visit [week 9]) on the School Version total score: modafinil/placebo, –15.1 (11.4); modafinil/modafinil, –18.4 (12.4); placebo/placebo, –10.2 (10.0). The improvements in patients' overall clinical condition documented by the CGI-I assessment were sustained during the 2-week observation period (CGI-I responders at week 9: 38% for modafinil/placebo, 40% for modafinil/modafinil, 13% for placebo/placebo).

Tolerability

Modafinil was well tolerated, with most adverse events reported being mild to moderate in nature. Tolerability profiles were similar between children < 30 kg and those ≥ 30 kg who received different absolute doses of modafinil in this study. Insomnia, headache, and decreased appetite

Figure 2. Teacher-/Investigator-Rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version Total Score by Visit During 7-Week Double-Blind Period



*p Values represent difference between modafinil and placebo in mean change from baseline.

were the most common adverse events during the 7-week double-blind phase (Table 3), but only insomnia and decreased appetite were reported at a significantly greater frequency with modafinil than with placebo. The proportions of patients reporting these adverse events in the modafinil group were slightly lower than in 2 other studies that used slower titration to the 340- and 425-mg doses.[35,36] A total of 37% of the patients receiving modafinil compared with 38% receiving placebo discontinued from the study; the reasons for discontinuation were different in the 2 respective groups (10% vs. 0% for adverse events and 13% vs. 27% for lack of efficacy). Adverse events leading to discontinuation (patients could discontinue because of 1 or more adverse events) were insomnia (N = 3); emotional lability and abdominal pain (N = 2, both); and headache, decreased appetite, tachycardia, leukopenia, agitation, anxiety, hallucinations, hypertonia, nervousness, suicidality, thinking abnormal, asthma, increased cough, and dyspnea (N = 1 for each). All were new events.

Insomnia was reported by 30 patients receiving modafinil during the 7-week double-blind phase. In 25 patients with insomnia (83%), the event was rated as mild or moderate in severity, and it was reported within the first 1 to 2 weeks of the study. For 21 patients with insomnia (70%), resolution occurred while they continued modafinil treatment. No patients in the placebo group reported insomnia. Eighteen patients (14%) who received modafinil reported decreased appetite, and all of the events were considered mild or moderate in severity. In 14 (78%) of these 18 patients, the event was reported within the first 1 to 2 weeks of the study, and for 11 (61%) of these 18 patients, the reported events resolved by the end of the study (week 7).

Table 2. Efficacy Outcomes of Children and Adolescents With ADHD Receiving Modafinil or Placebo[a]

	Modafinil (N = 120)		Placebo (N = 63)			
Variable	Baseline	Final Double-Blind Visit	Baseline	Final Double-Blind Visit	p Value[b]	CI[c]
ADHD-RS-IV School Version						
Total score	37.8 (8.9)	20.7 (13.1)	36.6 (9.2)	28.4 (12.7)	< .0001	–12.7 to –5.3
Inattention	21.9 (3.9)	12.5 (7.4)	21.0 (4.3)	15.6 (6.2)	< .001	–6.0 to –1.8
Hyperactivity-impulsivity	15.9 (7.8)	8.2 (7.3)	15.7 (7.1)	12.9 (8.0)	< .0001	–7.0 to –3.2
ADHD-RS-IV Home Version						
Total score	38.8 (8.9)	24.9 (13.8)	38.7 (10.6)	30.8 (14.8)	.001	–11.3 to –2.9
Inattention	21.4 (4.6)	14.0 (7.2)	21.4 (5.1)	17.4 (7.7)	< .001	–6.1 to –1.7
Hyperactivity-impulsivity	17.4 (6.3)	10.9 (7.6)	17.3 (7.2)	13.4 (8.2)	.004	–5.4 to –1.1
CPRS:R-S						
ADHD index	75.7 (7.4)	65.0 (11.3)	76.4 (9.5)	71.2 (12.2)	< .001	–10.1 to –3.2
Cognitive problems/inattention	74.0 (9.0)	64.0 (12.0)	75.2 (10.2)	71.1 (12.3)	< .0001	–10.5 to –3.7
Hyperactivity	75.7 (11.3)	63.9 (14.2)	75.2 (14.6)	70.6 (14.8)	< .001	–12.2 to –4.0

[a]Values represent mean (SD), except where noted.
[b]Values represent difference between modafinil and placebo in mean change from baseline to final double-blind period visit.
[c]95% CI of change from baseline for modafinil vs. placebo.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS-IV Home Version = parent-/investigator-rated ADHD Rating Scale-IV, ADHD-RS-IV School Version = teacher-/investigator-rated ADHD Rating Scale-IV, CI = confidence interval, CPRS:R-S = Conners' Parent Rating Scale-Revised, Short Form.

Two patients receiving modafinil experienced 3 serious adverse events (asthma attack, influenza syndrome, dehydration) during the double-blind phase. These events resolved spontaneously and were considered by the investigator to be "not related" or "unlikely related" to the study medication.

No statistically significant or clinically meaningful differences were observed in mean changes from baseline to final visit for heart rate or blood pressure (Table 4). Changes in body weight over the 7-week double-blind phase differed between the modafinil and placebo groups, with a mean increase of 1.0 kg for those who received placebo and a mean decrease of 0.6 kg for those who received modafinil ($p < .0001$). No patient had clinically significant weight loss when individual weights were corrected for age- and gender-specific means for the general pediatric and adolescent population. No clinically meaningful differences between the groups were observed in 12-lead ECG or laboratory parameters.

During the 2-week observation period, adverse events were reported by 11 patients (26%) who continued to receive modafinil (modafinil/modafinil), 10 patients (27%) who were switched to placebo after modafinil (modafinil/placebo), and 6 patients (15%) who continued to receive placebo (placebo/placebo). The events in the modafinil and placebo groups were similar to those reported in the respective groups during the 7-week double-blind phase (Table 5). No serious adverse events were reported and no patient discontinued because of an adverse event during the observation period.

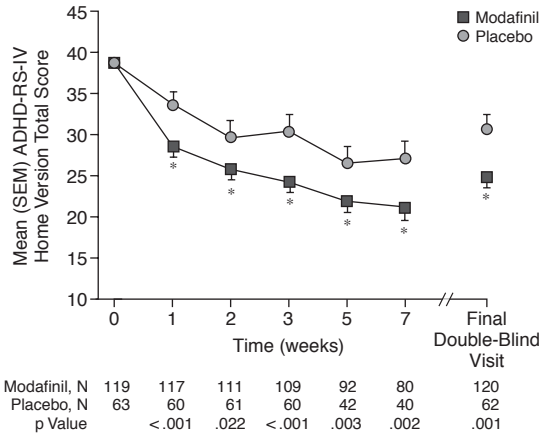
DISCUSSION

Modafinil significantly improved symptoms of ADHD, including inattention, hyperactivity, and impulsivity, compared with placebo in this double-blind study. The significant improvements in symptoms with modafinil occurred at each visit as shown by the reductions in total scores for both the School and Home Versions of the ADHD-RS-IV as well as inattention and hyperactivity-impulsivity subscale scores. In addition, modafinil significantly improved patients' overall clinical condition at each visit compared with placebo. These findings suggest consistent therapeutic effects of modafinil at school and home during weekdays, evenings, and weekends as evaluated by clinicians, teachers, and parents.

The onset of this effect of modafinil began early, with statistically significant differences observed at week 1 (starting at 85 mg and increasing every other day by 85 mg to a dose of 340 mg/day by the end of the week) for total scores on the ADHD-RS-IV School and Home Versions and on the CGI-I. For all 3 efficacy assessments, continued improvements were observed in the modafinil group (with an additional increase to 425 mg/day for those patients weighing 30 kg or more), but some improvement was also observed in patients receiving placebo. There was an increasing separation between patients receiving modafinil and placebo over the 7-week double-blind phase. These findings suggest that once-daily modafinil, when titrated over 7 to 9 days to doses of 340 mg or 425 mg based on body weight, reduces the symptoms of ADHD throughout the day (during the day at school as well as in the evening at home) and that the effect is maintained over time.

This study also examined the effect of abrupt discontinuation of modafinil. Although the primary purpose of the observation period of the study was to evaluate the effects of abrupt discontinuation, the study also provided an opportunity to evaluate the recurrence of symptoms of ADHD as well. Few well-controlled studies have investi-

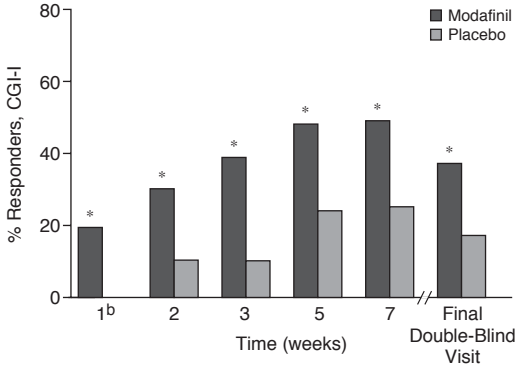
Figure 3. Parent-/Investigator-Rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) Home Version Total Score by Visit During 7-Week Double-Blind Period



Modafinil, N	119	117	111	109	92	80	120
Placebo, N	63	60	61	60	42	40	62
p Value		<.001	.022	<.001	.003	.002	.001

*p Values represent difference between modafinil and placebo in mean change from baseline.

Figure 4. Percentages of Patients Who Were Responders[a] as Measured by the Clinical Global Impressions-Improvement Scale (CGI-I) During 7-Week Double-Blind Period



Modafinil, N	117	110	109	92	80	120
Placebo, N	61	61	61	42	40	63
p Value	<.001	<.0001	<.0001	<.001	<.001	<.001

[a]Response defined as a CGI-I rating of "much improved" or "very much improved."
[b]At week 1, 0% of placebo patients were responders.
*p Values represent difference between modafinil and placebo.

gated abrupt discontinuation of medications for ADHD, but, in clinical practice, missed doses of CNS stimulants are thought to lead to worsening of behavior and attention due to rapid loss of efficacy and return toward baseline levels.[37,38] The results of this period of the study showed that abrupt discontinuation of modafinil after 7 weeks did not result in the emergence of acute symptoms of withdrawal or rebound effects (i.e., new adverse events). In addition, during the 2-week observation period, the ADHD-RS-IV School Version total score remained below baseline values. Some gradual recurrence of symptoms was observed during this period. Previous studies of abrupt discontinuation of stimulants have shown similar results.[39] This lack of symptoms of withdrawal and symptom rebound may result from a placebo effect following abrupt discontinuation; however, these results are consistent with the lack of abrupt discontinuation effects observed in patients taking modafinil for excessive sleepiness associated with narcolepsy.[18] In addition, atomoxetine has not been associated with symptoms of withdrawal or symptom rebound upon abrupt discontinuation during a 1-week observation period.[40]

In clinical studies, CNS stimulants have been associated with insomnia, decreased appetite, nervousness, and changes in heart rate and blood pressure.[41–44] Atomoxetine is also associated with cardiovascular effects, and gastrointestinal symptoms have been reported.[5,45] In this study, insomnia and decreased appetite were reported significantly more frequently with modafinil than placebo. These adverse events were generally mild to moderate in severity, and their occurrence decreased substantially after the first 2 weeks. Few patients discontinued therapy because of insomnia (N = 3) or decreased appetite (N = 1).

Table 3. Adverse Events of All Causes Experienced by ≥ 5% of Patients During 7-Week Double-Blind Period[a]

Adverse Event	Modafinil (N = 125)	Placebo (N = 64)
Insomnia[b]	30 (24)	0 (0)
Headache	21 (17)	9 (14)
Decreased appetite[c]	18 (14)	1 (2)
Infection	13 (10)	10 (16)
Abdominal pain	12 (10)	5 (8)
Fever	7 (6)	2 (3)
Increased cough	7 (6)	3 (5)
Rhinitis	5 (4)	5 (8)

[a]Values represent number (%) of patients.
[b]p < .0001 for modafinil vs. placebo.
[c]p = .0042 for modafinil vs. placebo.

In disorders of excessive sleepiness, modafinil does not interfere with sleep when sleep is needed, as assessed by polysomnography, and insomnia is not a commonly reported adverse event. Therefore, it is somewhat surprising that insomnia is a commonly reported adverse event in this study of children and adolescents with ADHD. This difference across disorders deserves additional evaluation to determine if this is a chance finding or can be replicated with a design that is equally sensitive to the assessment of insomnia. Modafinil did not result in any statistically significant or clinically meaningful effects on measures of cardiovascular function, including heart rate and blood pressure. A statistically significant difference between groups in mean changes in body weight was observed, but the magnitude of change was relatively small. No patient met the preset criteria for a clinically significant change in body weight during the 7-week double-blind phase.

Overall, 37% of patients receiving modafinil and 38% of those receiving placebo discontinued from this study. In pediatric clinical studies, the discontinuation rate is af-

Table 4. Vital Signs in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder Receiving Modafinil or Placebo[a]

	Modafinil (N = 125)		Placebo (N = 64)		
Variable	Baseline	Final Double-Blind Visit	Baseline	Final Double-Blind Visit	p Value[b]
Heart rate, bpm	80.5 (9.7)	82.6 (10.1)	82.1 (9.7)	82.8 (11.7)	.8864
Systolic blood pressure, mm Hg	105.3 (9.7)	102.7 (10.4)	103.0 (9.8)	103.1 (8.8)	.1006
Diastolic blood pressure, mm Hg	66.0 (6.7)	65.1 (7.7)	65.7 (7.3)	66.2 (6.6)	.0977

[a]Values represent mean (SD).
[b]For modafinil vs. placebo.

Table 5. Incidence of Adverse Events Experienced by ≥ 5% of Patients During 2-Week Observation Period[a]

Adverse Event	Modafinil/ Modafinil (N = 43)	Modafinil/ Placebo (N = 37)	Placebo/ Placebo (N = 40)
Headache	2 (5)	2 (5)	0 (0)
Abdominal pain	1 (2)	2 (5)	1 (3)
Contact dermatitis	0 (0)	2 (5)	0 (0)

[a]Values represent number (%) of patients.

fected by the study design, and particularly by options available following discontinuation.[46] In this study, patients had the option to switch to open-label treatment after week 4 but prior to the end of the study; the availability of a treatment with known efficacy may have been a factor that contributed to the discontinuation rate. Of those patients who discontinued during the study, 19 (42%) of 45 patients in the modafinil group and 15 (63%) of 24 patients in the placebo group entered the open-label extension study. While 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, in which 27% of patients reported lack of efficacy as the reason for discontinuation compared with only 13% in the modafinil group. In the modafinil group, 10% of patients discontinued because of adverse events. This rate is somewhat higher than those observed in 2 other flexible-dose studies (5% and 3%) of modafinil in children with ADHD that used a slower titration of 3 weeks.[35,36] However, the occurrence of specific adverse events (i.e., insomnia, decreased appetite, and headache) was equal or lower in this study (24%, 14%, and 17%, respectively) compared with the other studies (28%, 18%, and 22%, respectively, in one study[35] and 29%, 16%, and 20%, respectively, in the other[36]), suggesting that modafinil does not elicit a greater number of common adverse events associated with pharmacologic treatment of ADHD.

This study has several other limitations. The double-blind phase of 7 weeks was relatively short, and additional studies are needed to determine the longer-term efficacy and safety profile of modafinil in children and adolescents with ADHD. The TOVA was the only objective measure used to evaluate attention, but it may not provide a reliable measure of response to medication. This may be due to the length of time required to perform the test (20+ minutes) and carryover effects. In this study, neither the administration of modafinil nor the administration of placebo had a substantial impact on TOVA scores, as reflected by the change from baseline. In future studies, other objective tests that can be administered in a shorter time period and can be repeated over the multiple observation timepoints of a study would be more appropriate to evaluate the effects of modafinil on attention.

In conclusion, treatment of children with ADHD with modafinil was effective across the full spectrum of symptoms of ADHD, including inattention, hyperactivity, and impulsivity. Patients receiving modafinil had sustained improvements, as shown by significant improvements in teacher and parent ratings compared with patients receiving placebo throughout the 7-week double-blind phase. Following abrupt discontinuation of modafinil, symptoms of ADHD did not rebound to pretreatment values and remained below the levels of symptoms for patients who continued to receive placebo. Modafinil was generally well tolerated. The most common adverse events were generally manageable. There were no notable changes in cardiovascular measures or laboratory tests. Adverse events during the 2-week observation period were comparable to those during the double-blind phase of this study. These findings suggest that modafinil may provide a novel therapeutic option for the management of ADHD in pediatric and adolescent patients.

Drug names: amphetamine (Adderall and others), atomoxetine (Strattera), methylphenidate (Ritalin, Metadate, and others).

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