A Comparison of Once-Daily and Divided Doses of Modafinil in Children With Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-Blind, and Placebo-Controlled Study

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Objective: This randomized, double-blind, placebo-controlled study assessed the efficacy and tolerability of several modafinil dosing regimens in children with attention-deficit/hyperactivity disorder (ADHD) to determine whether modafinil can be given once daily in pediatric ADHD.

Method: Children and adolescents (age range, 6–13 years) (N = 248) with DSM-IV–defined ADHD were enrolled in a 4-week, double-blind, placebo-controlled study, conducted February–May 2002. The group was assigned to receive oral (100-mg tablets) modafinil 300 mg once daily (300 mg in the morning followed by placebo at midday), modafinil 300 mg as a divided dose (100/200 mg or 200/100 mg), or matching placebo. In children weighing ≥ 30 kg, a higher dose of 400 mg (200/200 mg) was evaluated. Efficacy measures included the teacher-rated School Version and clinician-rated Home Version of the ADHD Rating Scale-IV and the parent-completed Conners' ADHD/DSM-IV Scales.

Results: 223 children completed the study. Those who received modafinil 300 mg once daily showed a significantly greater improvement (change from baseline) than those who received placebo in symptoms of ADHD across all rating scales and subscales (all $p < .05$). Divided 300-mg doses of modafinil provided some significant but inconsistent improvements in ADHD symptoms. In children weighing ≥ 30 kg, modafinil 400 mg (200/200 mg) was significantly superior to placebo on clinician- and parent-completed scales (all $p < .05$). Insomnia was the only adverse event to occur with significantly greater frequency in a modafinil group (200/100) than in the placebo group (14% vs. 2%) ($p = .03$).

Conclusion: Modafinil significantly improved ADHD symptoms in children. Once-daily dosing (300 mg) provided the most consistent improvement in symptoms. All dosing regimens of modafinil were well tolerated.

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Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous syndrome estimated to affect 8% to 12% of school-aged children.[1] Behaviorally, ADHD is characterized by symptoms of inattention, impulsivity, and hyperactivity, which are evident across multiple settings. Pharmacotherapies used to manage core symptoms include central nervous system stimulants and the norepinephrine reuptake inhibitor atomoxetine.[2] However, for some children, the use of these agents may be limited by inadequate response or tolerability.

Modafinil, an attention-promoting agent, has been shown in animal studies to selectively activate neurons in both the tuberomammillary nucleus and lateral hypothalamus,[3–5] which have substantial projections through the cerebral cortex[6] that increase activity in key areas of the brain (anterior cingulate cortex[7] and frontal cortical areas[8]) thought to be important in the pathophysiology of ADHD. Modafinil is structurally and pharmacologically distinct from other pharmacologic agents used for ADHD. While modafinil has a long elimination half-life (15 hours) in adults, children may metabolize modafinil more quickly,[9] raising the issue of whether modafinil would be effective if given once daily in pediatric ADHD. Initial small-scale studies conducted in children with ADHD reported improvement in ADHD symptoms with once-daily modafinil.[10,11] Here, we report the results of a randomized, double-blind, placebo-controlled phase II study designed to assess the efficacy and safety of 3 dosing regimens of

modafinil 300 mg/day, administered once daily in the morning and in divided doses (morning and midday), in children with ADHD. The study was also designed to evaluate the effects of a higher dose (400 mg) in older children.

METHOD

Study Design

This randomized, placebo-controlled, parallel-group, phase II study was conducted at 28 centers in the United States between February 2002 and May 2002. The study included a 7- to 10-day, single-blind, placebo run-in phase that served as a washout for those patients previously taking psychostimulants, followed by a 4-week double-blind period during which children received modafinil or placebo. Children attended the clinic at screening, initiation of the placebo phase, and baseline and at 1-week intervals thereafter during the double-blind period. Before enrollment, each child provided assent, and written informed consent was obtained from the parent or legal guardian. The study was conducted in accordance with the ethical standards of each center's Institutional Review Board and the Declaration of Helsinki of 1975, as revised in 2000.

Patients

Children aged 6 to 13 years whose height and weight corresponded to greater than the fifth percentile in standardized growth charts and who were attending full-day kindergarten, elementary school, or middle school were eligible. Participants met complete criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), for ADHD (combined type, predominantly inattentive type, or predominantly hyperactive-impulsive type)[12] at screening, as determined by a psychiatric/clinical evaluation and confirmed by the Diagnostic Interview Schedule for Children, Fourth Edition.[13] Eligibility was restricted to those children who were stimulant-naive (i.e., who had not received stimulant medication in the past) or who had manifested an unsatisfactory response to stimulant therapy. At screening, an intelligence quotient (IQ) of at least 80, as estimated on the Wechsler Intelligence Scale for Children, Third Edition,[14] and a score of 80 or higher on the screener version (for learning disabilities) of the Wechsler Individual Achievement Test[15] were used to rule out low IQ or learning disabilities as contributing causes of symptoms and were required for inclusion. At the baseline visit, children were required to have a clinician-rated Clinical Global Impressions of Severity (CGI-S)[16] score of 4 or more, reflecting their overall clinical condition (moderately ill or worse). For each child, availability of a parent and a weekday teacher who were willing to participate in the study was required. Main exclusion criteria included active, clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematologic, neoplastic, endocrine, neurologic, immunodeficiency, pulmonary, or other major clinically significant disorder or disease; any current psychiatric comorbidity, including but not limited to depression or other mood disorder, anxiety disorder, or pervasive mental disorder that required pharmacotherapy; use of any prescription (e.g., clonidine, guanfacine) or nonprescription medication with psychoactive properties (e.g., over-the-counter medications or dietary supplements containing ephedrine, pseudoephedrine, caffeine, or phenylpropanolamine) within 1 week of the start of the washout period; and a history or evidence of substance abuse.

Procedures and Assessments

For the single-blind placebo washout, blister packs containing 5 tablets for daily administration were provided. Children were instructed to take 3 tablets in the early morning (between 0700 and 0800) and 2 tablets 4 to 5 hours later (between 1100 and 1300). At the end of the washout period, continued eligibility was determined, baseline assessments were performed, and children were randomized to receive modafinil or matching placebo. Throughout the double-blind period, children received 3 tablets in the early morning and 2 tablets 4 to 5 hours later, regardless of group, to maintain the blind. Each tablet contained modafinil (100 mg) or matching placebo.

A stratified schema based on body weight was used to randomize the participants. In the stratum defined by body weight < 30 kg, children were randomized with an equal chance to 1 of 4 groups: placebo, modafinil 300 mg in the morning followed by 0 mg at midday (modafinil 300 mg once daily), modafinil 100 mg followed by 200 mg (modafinil 100/200-mg divided dose), or modafinil 200 mg followed by 100 mg (modafinil 200/100-mg divided dose). In the stratum defined by body weight ≥ 30 kg, children were randomized to receive 1 of 5 conditions: the same 4 as the lower weight stratum with equal probability, and a higher dose of modafinil 200 mg in the morning followed by 200 mg at midday (modafinil 400 mg) at twice the probability of any of the other conditions. Thus, the relative weights for the 5 conditions were 1:1:1:1:0 for the lower weight stratum and 1:1:1:1:2 for the higher weight stratum. Modafinil doses were increased gradually according to the following schedule: all children in the modafinil arms received 100 mg on days 1–3; thereafter, daily doses increased by 100-mg increments according to a predetermined schedule (i.e., 200 mg/day, days 4–5; 300 mg/day, days 6–7; 400 mg/day, day 8) until the final assigned daily dose was reached. Study medication was provided to the child's parent or legal guardian for administration at home and to a school administrator or nurse for administration at school.

Efficacy was determined using the School and Home versions of the ADHD Rating Scale-IV (ADHD-RS-IV),[17] an 18-item instrument that assesses the occurrence of

individual criteria provided in the DSM-IV.[12] This rating scale has been shown to be sensitive to drug effects in children.[18] Individual items are scored using an ordinal scale (i.e., 0 = never or rarely, 1 = sometimes, 2 = often, or 3 = very often). Three scores can be derived: a total score (sum of 18 items), an inattention subscale score (sum of 9 items), and a hyperactivity-impulsivity subscale score (sum of 9 items). The School Version of the ADHD-RS-IV was completed by the child's regular teacher during the single-blind placebo washout and at weekly intervals during the double-blind period. If possible, a single teacher provided ratings for each child for the duration of the study. Teachers completed the scale twice a day, once in the morning and again in the afternoon, on 2 nonconsecutive days (e.g., Tuesday and Thursday). Weekly total and subscale scores for each child were obtained by first averaging scores across each day and then averaging daily scores across each week. The Home Version of the ADHD-RS-IV was completed by the child's physician or other qualified clinician (following an interview with the parent or legal guardian and the child whenever appropriate) at baseline and thereafter on a weekly basis.

Efficacy also was determined using the 26-item Parent Version of the Conners' ADHD/DSM-IV Scales (CADS-P).[19] Among the CADS-P specialty scales are the 12-item ADHD Index and the 18-item DSM-IV Symptoms Scale, with 9 inattentive and 9 hyperactive-impulsive items.[12] The CADS-P was completed at baseline and on a weekly basis during the double-blind period, with total scores, ADHD Index, and inattentive and hyperactive-impulsive subscale scores determined for each patient; t scores were summarized and analyzed.[19,20] Overall severity of ADHD was assessed at baseline using the physician-rated CGI-S, and changes in overall clinical condition were evaluated using the Clinical Global Impressions of Improvement (CGI-I).[16]

Safety was assessed by monitoring reported or observed adverse events according to group, type, day of onset, and severity. Clinical impressions were made regarding possible relationship to modafinil. Physical examinations and resting 12-lead electrocardiograms (ECGs) were conducted at the screening visit and at week 4. Weight, vital signs, and laboratory parameters were determined at screening, during the run-in/washout, at baseline, and at 1-week intervals thereafter.

Statistical Analysis

Sample size estimates were based on the anticipated change in the ADHD-RS-IV total score (clinician-rated Home Version). Assuming a standard deviation of 11 for a significance level of 5% on a 2-group t test, a sample size of 40 for each group was sufficient to provide 80% power to detect a between-group change from baseline difference of 7 points. The efficacy analyses prospectively specified that pairwise comparisons be made between placebo and each of the modafinil regimens. Comparisons between placebo and modafinil 400 mg were limited by study design to the stratum of children weighing ≥ 30 kg.

Table 1. Disposition of Patients[a]

	Modafinil Dose (mg morning/mg midday)				
Disposition	200/200 (N = 50)	200/100 (N = 49)	100/200 (N = 48)	300/0 (N = 50)	Placebo (N = 51)
Randomized	50	49	48	50	51
Safety analysis set	50 (100)	49 (100)	48 (100)	50 (100)	51 (100)
Efficacy analysis set	50 (100)	49 (100)	47 (98)	50 (100)	51 (100)
Completed study	46 (92)	45 (92)	40 (83)	44 (88)	48 (94)
Discontinued study	4 (8)	4 (8)	8 (17)	6 (12)	3 (6)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse event	1 (2)	2 (4)	4 (8)	2 (4)	0 (0)
Lack of efficacy	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)
Consent withdrawn	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)
Protocol violation	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Noncompliance	0 (0)	0 (0)	1 (2)	1 (2)	1 (2)
Lost to follow-up	1 (2)	1 (2)	2 (4)	0 (0)	0 (0)
Disease progression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)

[a]All values are number (percentage) of children.

The 5 randomly assigned groups were expected to have equal representation with regard to age and weight (i.e., placebo and modafinil groups receiving 300 mg once daily or divided dose). Patients that received at least 1 dose of study drug and had at least 1 postbaseline efficacy measurement were included in the efficacy analyses. Because the modafinil 400-mg group was limited to the stratum of children weighing ≥ 30 kg, all comparisons involving this group were limited to children who weighed ≥ 30 kg, received at least 1 dose of modafinil, and had at least 1 postbaseline efficacy measurement.

Efficacy variables included the mean change from baseline to the final visit (i.e., week 4 or termination visit) in the total and subscale scores of the ADHD-RS-IV (School and Home versions) and the CADS-P. Group differences were assessed using analysis of covariance (ANCOVA), with treatment as a factor and baseline score as a covariate. Pairwise comparisons between modafinil and placebo were conducted using least squares means derived from the ANCOVA model. CGI-I data were analyzed using a Cochran-Mantel-Haenszel χ^2 test. Statistical tests were 2-tailed, with the level of significance set at 5%.

Children who received at least 1 dose of medication were evaluated for safety. Safety data were included in descriptive statistical summaries. Comparisons of adverse events between modafinil and placebo groups were performed using a Fisher exact test. Between-group differences in weight and vital signs were analyzed using the Kruskal-Wallis test.

Table 2. Baseline Characteristics and Severity/Symptom Scores

Characteristic	Modafinil Dose (mg morning/mg midday) 300/0 (N = 50)	200/100 (N = 49)	100/200 (N = 48)	200/200 (N = 50)	Placebo (N = 51)
Age, mean (SD), y	8.8 (2.0)[a]	8.8 (2.1)	9.2 (2.1)	10.5 (1.6)	8.9 (2.0)
Gender, male/female, N (%)/N (%)	33 (66)/17 (34)	39 (80)/10 (20)	38 (79)/10 (21)	37 (74)/13 (26)	38 (75)/13 (25)
Ethnicity, N (%)					
White	40 (80)	41 (84)	38 (79)	41 (82)	42 (82)
Other	10 (20)	8 (16)	10 (21)	9 (18)	9 (18)
Height, mean (SD), cm	136.3 (11.9)	135.7 (13.9)	137.5 (13.9)	144.9 (9.1)	136.3 (13.1)
Weight, mean (SD), kg	34.8 (13.0)	36.9 (14.6)	36.9 (14.8)	42.0 (10.0)	33.6 (11.2)
Current ADHD subtype, N (%)					
Combined	42 (84)	40 (82)	38 (79)	33 (66)	37 (73)
Inattentive	7 (14)	7 (14)	9 (19)	17 (34)	11 (22)
Hyperactive-impulsive	1 (2)	1 (2)	1 (2)	0 (0)	2 (4)
CGI-S, N (%)					
Moderately ill	17 (34)	22 (45)	19 (40)	24 (48)	25 (49)
Markedly ill	26 (52)	24 (49)	24 (50)	21 (42)	23 (45)
Severely ill	7 (14)	2 (4)	4 (8)	5 (10)	3 (6)
Among the most extremely ill	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
ADHD-RS-IV, mean (SD), score					
School Version[b]					
Total	27.3 (14.1)	27.7 (13.5)	25.5 (14.1)	23.0 (11.4)	24.5 (13.8)
Inattention	15.0 (7.3)	15.9 (6.8)	15.1 (7.7)	13.7 (6.2)	13.3 (7.1)
Hyperactivity-impulsivity	12.7 (8.3)	12.0 (7.8)	10.9 (7.7)	9.7 (6.6)	11.6 (7.7)
Home Version[c]					
Total	36.5 (10.2)	37.6 (9.4)	36.8 (9.3)	34.0 (10.9)	35.5 (8.9)
Inattention	19.7 (5.0)	20.3 (5.0)	20.3 (4.6)	19.4 (5.9)	19.4 (4.3)
Hyperactivity-impulsivity	16.8 (6.6)	17.3 (5.7)	16.4 (6.7)	14.6 (6.5)	16.1 (6.2)
CADS-P, mean (SD), score (t score)					
Total[d]	74.3 (9.8)	76.2 (10.6)	75.1 (9.6)	74.1 (11.2)	73.4 (10.9)
ADHD Index[e]	73.0 (8.0)	73.1 (9.3)	73.6 (8.1)	72.6 (9.4)	73.4 (9.2)
Inattentive[d]	72.9 (9.4)	72.6 (10.6)	72.3 (8.9)	71.3 (10.2)	71.5 (10.2)
Hyperactive-impulsive[d]	72.8 (12.0)	77.0 (10.9)	74.0 (12.8)	73.3 (12.7)	72.2 (13.5)

[a]One child was 14 years of age, outside the protocol-specified range (6–13 y).
[b]Modafinil 300/0 mg, N = 49; modafinil 200/100 mg, N = 49; modafinil 100/200 mg, N = 45; modafinil 200/200 mg, N = 48; placebo, N = 48.
[c]Modafinil 300/0 mg, N = 49; modafinil 200/100 mg, N = 49; modafinil 100/200 mg, N = 46; modafinil 200/200 mg, N = 49; placebo, N = 51.
[d]Modafinil 300/0 mg, N = 49; modafinil 200/100 mg, N = 48; modafinil 100/200 mg, N = 47; modafinil 200/200 mg, N = 48; placebo, N = 48.
[e]Modafinil 300/0 mg, N = 49; modafinil 200/100 mg, N = 48; modafinil 100/200 mg, N = 47; modafinil 200/200 mg, N = 48; placebo, N = 50.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale-IV; CADS-P = Conners' ADHD Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Scales–Parent Version; CGI-S = Clinical Global Impressions of Severity.

RESULTS

Of 343 children screened, 248 were randomized (Table 1): 50 children were randomized to the 300-mg once daily dose; 49 were randomized to the 200/100-mg dose; 48 were randomized to the 100/200-mg dose; 50 were randomized to the 400-mg dose; and 51 were randomized to placebo. Baseline characteristics of the children randomly assigned to 1 of the 5 conditions are shown in Table 2. These patients ranged in age from 6 to 14 years. More boys than girls (75% vs. 25%) participated in the study, with ratios similar across groups. Demographic variables were analyzed according to body weight, with no significant differences observed among the 300-mg dose regimens. The group assigned to receive modafinil 400 mg was older and weighed more, in accordance with the protocol requirement that all children randomized to this group should weigh ≥ 30 kg; thus, differences in mean age, height, and weight were demonstrated between this group and others. The majority of patients (190/248 [77%]) met criteria for the ADHD combined subtype. Before the study, 77 (31%) had taken stimulants for ADHD within 30 days of screening, with methylphenidate being the most commonly used medication. On study entry, 91% (225/248) were moderately or markedly ill, and 9% (23/248) were severely ill or worse, based on the investigator-rated CGI-S. Mean baseline scores for each of the symptoms and subscales were comparable across the groups.

A total of 223 patients (90%) completed the study. Twenty-two (11%) randomized to modafinil discontinued the study for the following reasons: adverse event (N = 9), insufficient efficacy (N = 2), loss to follow-up (N = 4), noncompliance (N = 2), consent withdrawn (N = 2), protocol violation (N = 1), and other (N = 2). Three (6%) randomized to placebo discontinued: 2 because of insufficient efficacy and 1 because of noncompliance.

Efficacy Outcomes

Data from 196 patients randomized to receive placebo or modafinil 300 mg/day once daily or as a divided dose were analyzed for efficacy (modafinil groups vs.

placebo). There were no between-group differences with respect to any demographic parameter, including mean (SD) age (8.9 [2.1] years), height (136.4 [13.1] cm), or weight (35.5 [13.4] kg).

ADHD Rating Scale-IV (School Version). The group assigned to modafinil 300 mg once daily had improved symptoms of ADHD on this rating scale (Figure 1A), as shown by significantly greater reductions than placebo from baseline to the final visit in the mean total score ($p = .006$), inattention subscale score ($p = .004$), and hyperactivity-impulsivity subscale score ($p = .02$). The group assigned to modafinil 200/100-mg divided dose showed significantly greater decreases from baseline than placebo in the mean total score ($p = .03$) and the hyperactivity-impulsivity subscale score ($p = .04$). The group assigned to modafinil 100/200-mg divided dose did not show statistically significant reductions in scores on this rating scale.

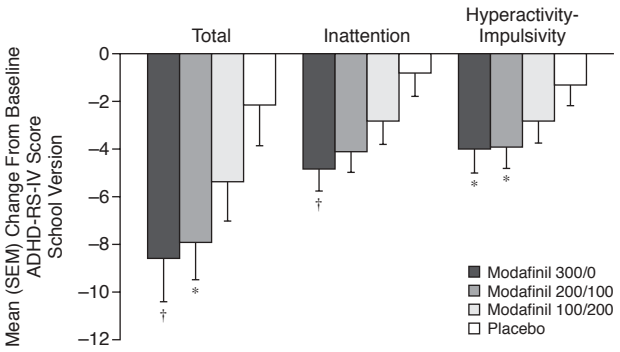
ADHD Rating Scale-IV (Home Version). Modafinil-related improvements in ADHD symptoms on the Home Version of the ADHD-RS-IV were consistent with improvements shown on the School Version (Figure 1B). Significantly greater reductions from baseline to the final visit than placebo in the mean total score ($p = .0006$), inattention subscale score ($p = .002$), and hyperactivity-impulsivity subscale score ($p = .001$) were shown in the modafinil 300-mg group. The group assigned to modafinil 200/100-mg divided dose had a significantly decreased hyperactivity-impulsivity subscale score ($p = .048$ vs. placebo). No significant reductions in scores on this rating scale were shown for the group assigned to modafinil 100/200-mg divided dose.

Conners' ADHD/DSM-IV Rating Scales. The group assigned to modafinil 300 mg once daily had improved ADHD symptoms on this rating scale (Figure 1C), as shown by significantly greater reductions from baseline to the final visit than placebo in the mean ADHD Index score ($p = .04$), total score ($p = .01$), inattentive subscale score ($p = .02$), and hyperactive-impulsive subscale score ($p = .02$). The group who received modafinil 200/100-mg divided dose had a significantly greater decrease from baseline than placebo in the hyperactive-impulsive subscale score ($p = .03$). The group assigned to receive modafinil 100/200-mg divided dose had significantly greater reductions than placebo in the mean total score ($p = .01$), inattentive subscale score ($p = .049$), and hyperactive-impulsive subscale score ($p = .01$).

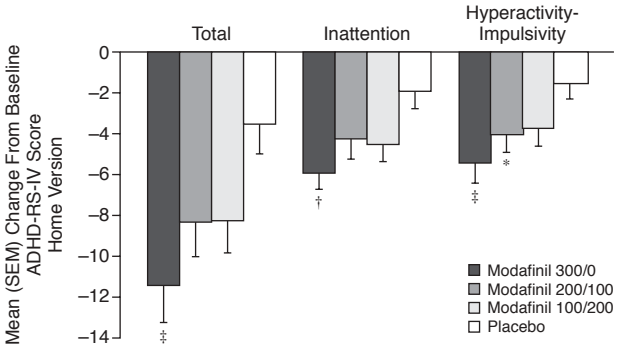
Clinical Global Impressions of Improvement. The percentages of patients rated by the investigator as clinically improved (i.e., much improved or very much improved) were greater for each modafinil 300-mg group (300 mg once daily, 30%; 200/100-mg divided dose, 33%; and 100/200-mg divided dose, 30%) compared with placebo (18%), although differences were not statistically significant.

Figure 1. Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 300-mg Modafinil Dosing Groups

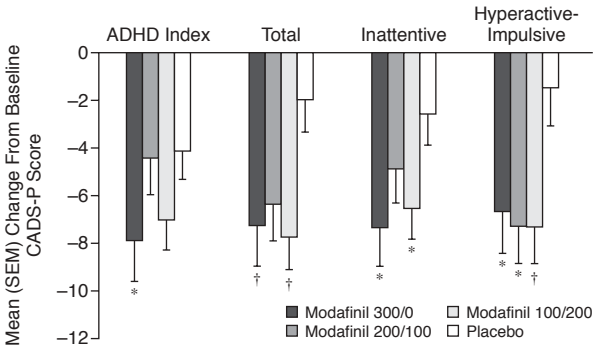
A. Teacher-Rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) (School Version)



B. Clinician-Rated ADHD Rating Scale-IV (ADHD-RS-IV) (Home Version)



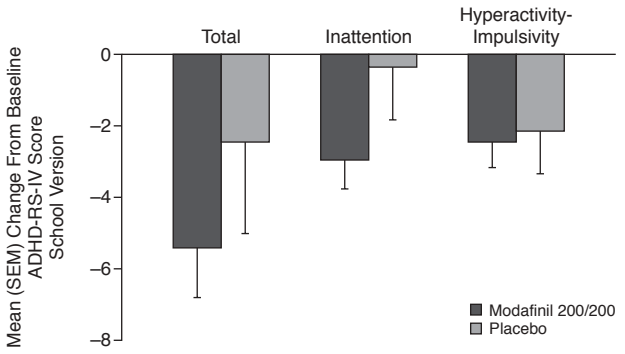
C. Conners' ADHD Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Scales–Parent Version (CADS-P)



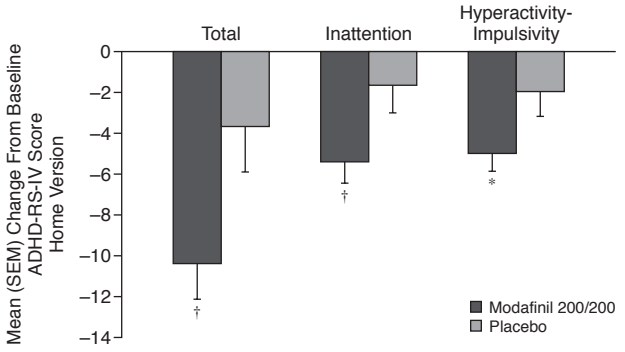
*$p < .05$; †$p \leq .01$; ‡$p \leq .001$ versus placebo.

Figure 2. Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 400-mg Modafinil Dosing Group

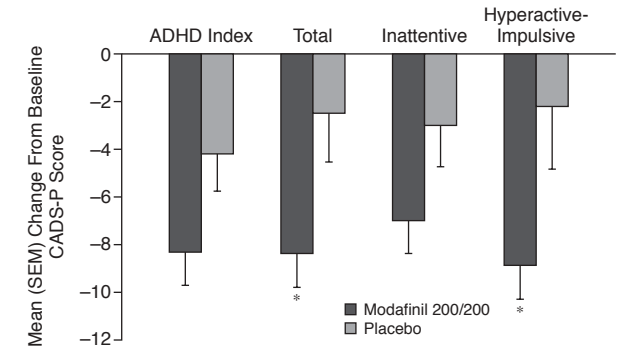
A. Teacher-Rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) (School Version)



B. Clinician-Rated ADHD Rating Scale-IV (ADHD-RS-IV) (Home Version)



C. Conners' ADHD Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Scales–Parent Version (CADS-P)



*p < .05; †p = .01 versus placebo.

Table 3. Adverse Events of All Causes Experienced by ≥ 10% of Patients in Any Group[a]

	Modafinil (mg morning/mg midday)				
Adverse Event	200/200 (N = 50)	200/100 (N = 49)	100/200 (N = 48)	300/0 (N = 50)	Placebo (N = 51)
Headache	7 (14)	6 (12)	6 (13)	7 (14)	11 (22)
Insomnia	5 (10)	7 (14)*	6 (13)	5 (10)	1 (2)
Infection	3 (6)	1 (2)	3 (6)	4 (8)	6 (12)
Pain (abdominal)	3 (6)	5 (10)	6 (13)	4 (8)	4 (8)
Cough	2 (4)	2 (4)	3 (6)	6 (12)	2 (4)
Rhinitis	2 (4)	0 (0)	5 (10)	2 (4)	2 (4)
Decreased appetite	1 (2)	4 (8)	3 (6)	6 (12)	1 (2)
Fever	0 (0)	5 (10)	5 (10)	2 (4)	2 (4)

[a]All values are number (percentage) of patients; the number of patients includes randomized patients who received at least 1 dose of study drug.
*p < .05, modafinil 200/100-mg divided dose versus placebo.

Other comparisons. In the subset of children weighing ≥ 30 kg (N = 158), additional analyses were performed to compare modafinil 400 mg (200/200) (N = 49) with placebo (N = 27). No significant differences were shown between the groups assigned to modafinil 400 mg and placebo for any score of the teacher-rated School Version of the ADHD-RS-IV (Figure 2A). The group assigned to modafinil 400 mg had improved ADHD symptoms on the clinician-rated Home Version of the ADHD-RS-IV, as shown by significant reductions from baseline to the final visit in the mean total score (p = .01), inattention subscale score (p = .01), and hyperactivity-impulsivity subscale score (p = .03) (Figure 2B). Improvements also were observed on the total score (p = .02) and hyperactive-impulsive subscale score (p = .02) of the CADS-P (Figure 2C).

Safety Outcomes

All dosing regimens of modafinil were well tolerated. Adverse events of all causes that occurred in ≥ 10% of patients in any group and were reported more frequently in modafinil groups than in the placebo group were insomnia, pain, cough, decreased appetite, fever, and rhinitis (Table 3). Insomnia was the only adverse event that occurred with significantly greater prevalence in a group assigned to modafinil (200/100-mg divided dose) than in the placebo group (p = .03). One child who received modafinil 400 mg experienced serious dehydration, gastroenteritis, and vomiting on day 14; these adverse events were considered by the investigator to be unrelated to modafinil. No other serious adverse events were reported. There were no clinically or statistically significant effects of modafinil on weight compared with placebo (final visit, range of mean [SD] changes for the modafinil groups, –0.4 [1.0] kg to –1.0 [1.1] kg vs. placebo, 0.7 [1.1] kg) (p > .05). Modafinil had no clinically significant effect on laboratory values or cardiovascular parameters, including those obtained from ECGs, blood pressure readings, or pulse measurements. Differences between

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Table 4. Changes From Baseline to the Final Visit in Vital Signs[a]

Parameter	Modafinil (mg morning/mg midday) 200/200 (N = 50)	200/100 (N = 49)	100/200 (N = 48)	300/0 (N = 50)	Placebo (N = 51)	p Value
Systolic blood pressure (mm Hg)						
Baseline value	106.5 (10.2)	104.4 (9.7)	102.5 (8.5)	102.6 (9.8)	102.7 (8.5)	
Final-visit value	105.5 (9.5)	103.4 (9.6)	103.3 (10.0)[b]	102.0 (8.0)	102.2 (10.7)	
Change	–1.0 (9.5)	–1.0 (8.9)	0.7 (8.5)[b]	–0.6 (7.5)	–0.6 (11.2)	> .05
Diastolic blood pressure (mm Hg)						
Baseline value	63.7 (7.0)	65.8 (10.4)	63.8 (6.8)	64.5 (6.8)	63.7 (6.1)	
Final-visit value	64.5 (7.4)	63.4 (9.9)	63.4 (6.5)[b]	64.6 (7.8)	63.2 (7.9)	
Change	0.8 (8.7)	–2.4 (10.6)	–0.4 (6.9)[b]	0.1 (8.8)	–0.5 (9.6)	> .05
Pulse (bpm)						
Baseline value	84.1 (10.7)	85.0 (11.2)	81.0 (11.0)	85.5 (10.5)	84.3 (11.5)	
Final-visit value	85.0 (11.4)	86.0 (11.8)	86.3 (14.4)[b]	88.5 (12.2)	83.3 (10.4)	
Change	0.9 (11.9)	1.0 (12.2)	5.2 (15.3)[b]	3.0 (11.9)	–1.0 (11.0)	> .05

[a]All values are mean (SD).
[b]N = 47.

modafinil and placebo in mean change-from-baseline final values for systolic or diastolic blood pressure or pulse rate were not statistically or clinically significant (Table 4) (all $p > .05$).

The percentage of patients receiving modafinil who discontinued the study because of adverse events was low (4%) but greater than placebo (0%). Two patients receiving modafinil 300 mg once daily, 4 patients receiving modafinil 100/200-mg divided dose, 2 patients receiving modafinil 200/100-mg divided dose, and 1 patient receiving modafinil 400 mg withdrew from the study because of adverse events. Adverse events leading to discontinuation that were experienced by more than 1 patient included rash (N = 4) and decreased appetite (N = 2).

DISCUSSION

In this 4-week, randomized, double-blind, placebo-controlled study, modafinil was shown to improve the full spectrum of ADHD symptoms on rating scales completed by teachers, clinicians, and parents. Of the dosing regimens evaluated, only modafinil 300 mg once daily significantly improved symptoms across all scales and subscales compared with placebo (all $p < .05$), suggesting that once-daily administration of modafinil is effective across the day.

In contrast to modafinil 300 mg administered as a single dose in the morning, administration of modafinil 300 mg as divided doses (200/100 mg and 100/200 mg) in the morning and at midday did not consistently improve symptoms across all scales and subscales when compared with placebo. One explanation for this difference is that the larger morning dose of modafinil of 300 mg afforded greater pharmacodynamic effects during the course of the school day. Other factors that may have influenced outcomes observed with divided modafinil doses include the different times that the tests were administered (morning, afternoon, or late afternoon) and the different perceptions of those administering the tests (teacher, clinician, and parent).

A relatively high percentage of children receiving modafinil 400 mg (who were older and heavier) had the inattentive type of ADHD. In this subset of children weighing ≥ 30 kg, modafinil 400 mg was significantly superior to placebo on the Home Version of ADHD-RS-IV (total, inattention, and hyperactivity-impulsivity scores) and the CADS-P (total and hyperactive-impulsive scores) (all $p < .05$). Because comparisons with modafinil 400 mg were limited by study design to the stratum of children weighing ≥ 30 kg, it was not possible to compare the 200/200-mg group directly with the 300-mg groups (i.e., because insufficient numbers of children who weighed ≥ 30 kg received 300-mg doses: 300/0 mg, N = 28; 200/100 mg, N = 28; 100/200 mg, N = 25). In addition, the highest daily dose of modafinil 400 mg was administered as a divided dose only, further complicating comparison with the 300-mg once-daily dose.

Modafinil had no notable effect on body weight or any mean cardiovascular parameters, including blood pressure, heart rate, and ECG parameters. All cases of decreased appetite were considered to be mild to moderate. In this study, only 1 adverse event (insomnia) was shown to occur with significantly greater frequency in a modafinil group (200/100-mg divided dose) than in the placebo group.

The current study was designed to assess whether modafinil can be given once daily in pediatric ADHD. The formulation of modafinil used in this study was the 100-mg formulation, which has also been shown to improve ADHD symptoms in children in 2 small-scale studies.[10,11] Previous work on dose-response effects of modafinil in ADHD has suggested that doses below 200 mg are suboptimal and that doses higher than 200 mg may be necessary to achieve significant clinical improvements in symptoms of ADHD.[21] The results suggest that modafinil once daily can significantly improve symptoms of ADHD for 4 weeks.

Pharmacokinetic results from a preliminary 4-week, open-label study indicated a time-dependent reduction in systemic exposure of modafinil because of auto-induction of modafinil metabolism,[9] implying a higher dose of modafinil over time was needed to maintain the clinical response seen here. The systemic exposure required to obtain these results was determined to be 150 μg•h/mL. A new formulation, film-coated modafinil tablets at doses of 340 mg for patients weighing < 30 kg and 425 mg for patients weighing ≥ 30 kg, was developed to ensure the target systemic exposure and a robust clinical response over time. Large-scale, 9-week, double-blind, placebo-controlled studies evaluated this new formulation of modafinil. These studies reported that the target systemic exposure was achieved and that modafinil was well tolerated[22–24] and improved the full spectrum of ADHD symptoms in children and adolescents as well as their overall condition.

The study was limited to an evaluation of children and young adolescents. Thus, the results may not apply to older adolescents and adults. The study was not designed to analyze dose-dependent effects. Its 4-week duration precludes application to long-term clinical use. Additional studies that examine the efficacy and tolerability of modafinil over a longer term are warranted.

In summary, the results of this study suggest that modafinil administered as a single morning dose of 300 mg is an efficacious option for ADHD symptoms in children and young adolescents. All dosing regimens of modafinil were well tolerated. These results support the need for additional controlled clinical trials to establish the safety and efficacy of modafinil in ADHD (at 340 mg and 425 mg), which recently were completed.[22–24]

Drug names: atomoxetine (Strattera), caffeine (Cafcit), clonidine (Catapres, Duraclon, and others), guanfacine (Tenex and others), methylphenidate (Ritalin, Concerta, and others), modafinil (Provigil).

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REFERENCES

1. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005;366:237–248
2. Rappley MD. Clinical practice: attention deficit-hyperactivity disorder. N Engl J Med 2005;352:165–173
3. Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. Proc Natl Acad Sci U S A 1996;93:14128–14133
4. Engber TM, Koury EJ, Dennis SA, et al. Differential patterns of regional c-Fos induction in the rat brain by amphetamine and the novel wakefulness-promoting agent modafinil. Neurosci Lett 1998;241:95–98
5. Scammell TE, Estabrooke IV, McCarthy MT, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J Neurosci 2000;20:8620–8628
6. Baumann CR, Bassetti CL. Hypocretins (orexins) and sleep-wake disorders. Lancet Neurol 2005;4:673–682
7. Konrad K, Neufang S, Hanisch C, et al. Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study. Biol Psychiatry 2006;59:643–651
8. Zang YF, Jin Z, Weng XC, et al. Functional MRI in attention-deficit hyperactivity disorder: evidence for hypofrontality. Brain Dev 2005;27: 544–550
9. Owen J, Grasela T, Robertson P Jr, et al. Population pharmacokinetics of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. Presented at the American Association of Pharmaceutical Scientists; November 6–10, 2005; Nashville, Tenn
10. Rugino TA, Copley TC. Effects of modafinil in children with attention-deficit/hyperactivity disorder: an open-label study. J Am Acad Child Adolesc Psychiatry 2001;40:230–235
11. Rugino TA, Samsock TC. Modafinil in children with attention-deficit hyperactivity disorder. Pediatr Neurol 2003;29:136–142
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
13. Columbia University DISC Development Group. Diagnostic Interview Schedule for Children: Interviewer's Manual. 4th ed. New York, NY: Columbia University; 1999
14. Wechsler D. Wechsler Intelligence Scale for Children. 3rd ed. New York, NY: Harcourt Brace Jovanovich, Inc; 1992
15. Wechsler Individual Achievement Test Screener Manual. New York, NY: Harcourt Brace Jovanovich, Inc; 1992
16. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
17. DuPaul GJ, Power TJ, Anastopoulos AD, et al. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation. New York, NY: Guilford Press; 1998
18. Barkley RA. Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. New York, NY: Guilford Press; 1990

19. Conners CK, Sitarenios G, Parker JD, et al. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 1998;26:257–268
20. Conners CK. Conners' Rating Scales, Revised: Technical Manual. North Tonawanda, NY: Multi-Health Systems, Inc.; 2000
21. Swanson JM, Greenhill LL, Biederman J. Modafinil in children with ADHD: a randomized, placebo-controlled study. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
22. Biederman J, Swanson JM, Wigal SB, et al. 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. Pediatrics 2005;116:e777–e784
23. Greenhill LL, Biederman J, Boellner SW, et al. A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2006;45:503–511
24. Swanson JM, Greenhill LL, Lopez FA, et al. 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. J Clin Psychiatry 2006;67:137–147