Modafinil Improves Symptoms of Attention-Deficit/Hyperactivity Disorder across Subtypes in Children and Adolescents

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Objective This secondary analysis evaluated the efficacy of modafinil in children and adolescents by subtype of attention-deficit/hyperactivity disorder (ADHD) using pooled data from 3 double-blind, placebo-controlled studies.

Study design The patients were boys and girls age 6 to 17 years. ADHD subtype diagnoses (ie, inattentive, hyperactive-impulsive, combined) were based on criteria published in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). Patients received modafinil (170 to 425 mg) or placebo once daily for 7 to 9 weeks. Efficacy assessment used the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School and Home Versions, Clinical Global Impression of Improvement scale (CGI-I), and Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).

Results A total of 638 patients received modafinil (n = 423) or placebo (n = 215). The inattentive, hyperactive-impulsive, and combined subtypes included 187 (30%), 27 (4%), and 403 (65%) patients, respectively. Modafinil (vs placebo) significantly improved mean total scores for the ADHD-RS-IV School and Home Versions for the inattentive (change from baseline: School, modafinil, −15.7, placebo, −7.1; Home, modafinil, −13.8, placebo, −5.9) and combined subtypes (School, −16.5 vs −8.8; Home, −15.7 vs −7.6). Modafinil was associated with greater improvements on the CGI-I and improved CPRS-R:S subscale scores in inattentive and combined subtypes.

Conclusions Modafinil improved ADHD symptoms and behaviors in patients with the inattentive and combined subtypes as determined by teachers, investigators, and parents. *(J Pediatr 2008;152:394-9)*

Attention-deficit/hyperactivity disorder (ADHD), a chronic and disabling disorder beginning in childhood, is characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity, which may affect behavior and performance at school and at home.[1] Three distinct ADHD subtypes—inattentive, hyperactive-impulsive, and combined—were developed empirically.[2-4] Based on the preponderance of symptoms, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) recognizes these 3 ADHD subtypes. Although multiple pharmacotherapies are currently used to manage ADHD, few controlled studies have examined the efficacy of these agents by ADHD subtype.[5-7] Modafinil differs structurally and pharmacologically from other agents used to treat ADHD. In animal models, modafinil has been found to selectively activate neurons in the tuberomammillary nucleus and the perifornical area of the lateral hypothalamus.[8,9] Histaminergic and hypocretinergic projections from these areas are believed to enhance the activity of the anterior cingulate and frontal cortical regions,[10] which are believed to be important in the pathophysiology of ADHD.[11,12]

Modafinil film-coated tablets (340 or 425 mg/day) were evaluated in 3 double-blind, placebo-controlled studies[13-15] and found to be well tolerated and to improve the

ADHD	Attention-deficit/hyperactivity disorder	CI	Confidence interval
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV	CPRS-R:S	Conners' Parent Rating Scale-Revised: Short Form
CGI-I	Clinical Global Impression of Improvement	DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
CGI-S	Clinical Global Impression of Severity of Illness	SEM	Standard error of the mean

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symptoms of ADHD at home and at school. The present retrospective analysis used data pooled from these 3 studies to evaluate the efficacy of modafinil in children and adolescents by ADHD subtype.

METHODS

Patients

Complete inclusion and exclusion criteria were described previously.[13-15] Briefly, patients were girls and boys age 6 to 17 years who met the DSM-IV criteria for ADHD.[16] Additional key inclusion criteria included a Clinical Global Impression of Severity of Illness (CGI-S)[17] rating ≥4 (moderately ill or worse) and a total and/or subscale score on the Attention Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV)[18] ≥1.5 standard deviations above normal values for the same age and sex. The CGI-S is a standardized scale allowing a clinician to rate a patient's condition at baseline according to 7 categories: 1 = normal; 2 = borderline; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill.

Patients with a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV Axis I); those considered at risk for suicide; and those with other current psychiatric comorbidity that required pharmacotherapy were excluded.

Study Design

Data were pooled from 2 9-week, randomized, double-blind, placebo-controlled, flexible-dose (170 to 425 mg once daily) studies[14,15] and 1 7-week, randomized, double-blind, placebo-controlled, fixed-dose (340 or 425 mg once daily) study.[13] Results for the first 7 weeks are based on data from all 3 studies; results for weeks 8 and 9 are based only on the 2 9-week flexible-dose studies. Patients in all 3 studies who completed at least 4 weeks of double-blind treatment without withdrawing due to an adverse event were eligible to enter a 1-year open-label extension before the end of the study.

Efficacy Assessments

The primary efficacy measure in all 3 studies was the mean change from baseline to final visit in total score on the teacher-/investigator-rated ADHD-RS-IV School Version.[18] This scale assesses each of the 18 symptoms in the DSM-IV diagnostic criteria for ADHD; thus, the total score accounts for inattentive, hyperactive, and impulsive symptoms. The primary efficacy analysis included data from patients who received at least 1 dose of study medication and had at least 1 postbaseline assessment of the primary efficacy measure. The last-observation-carried-forward method was used to determine the values for "final visit."

Secondary efficacy measures included the ADHD-RS-IV Home Version[18] and Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).[19] CPRS-R:S results were scaled into T-scores with an age- and-sex adjusted norm of 50 and a standard deviation of 10. In general, T-scores >60 indicate increasing degrees of abnormality, ranging upward from 61 (mildly atypical) to scores >70 (markedly atypical).[20]

In a separate analysis, ADHD-RS-IV School and Home Version results were converted to percentile scores based on age and sex norms, with percentiles >85 considered definitive of ADHD. Change in overall clinical condition was assessed by investigators using the Clinical Global Impression of Improvement scale (CGI-I).[17] Responders were defined as patients with investigator ratings of "much improved" or "very much improved" on the CGI-I at final visit.

Statistical Analyses

Efficacy assessments were based on patients who received at least 1 dose of study drug and had at least 1 postbaseline total score for the ADHD-RS-IV School Version. For this pooled analysis, data from 3 patient populations were compiled: patients diagnosed with predominantly inattentive subtype ADHD, patients diagnosed with predominantly hyperactive-impulsive subtype ADHD, and patients diagnosed with combined subtype ADHD. Data for the ADHD-RS-IV and the CPRS-R:S were grouped by subtype, and the 95% confidence intervals (CIs) for the change from baseline were constructed using t statistic. For the CGI-I ratings, 95% CIs were constructed using normal approximations.

RESULTS

Patients

In the 3 pivotal studies, 638 patients were randomized to modafinil (n = 423) or placebo (n = 215). Patients who received at least 1 dose of study drug and had at least 1 postbaseline total score for the ADHD-RS-IV School Version (modafinil, n = 411; placebo, n =210) were included in the efficacy analysis (Figure 1; available at www.jpeds.com). Demographics and baseline disease characteristics for this population are summarized in Table I. A total of 187 patients (30%) were diagnosed with predominantly inattentive subtype ADHD, 27 patients (4%) were diagnosed with predominantly hyperactive-impulsive subtype ADHD, and 403 patients (65%) were diagnosed with the combined subtype ADHD. A greater proportion of patients were rated as severely or extremely ill in the combined group (18%) than in the inattentive group (5%) or in the hyperactive-impulsive group (7%). A majority (69%) of the 505 patients who ultimately entered the open-label extension did not exercise their option to move into the extension after 4 weeks of double-blind treatment.

Efficacy

Mean total scores on the ADHD-RS-IV School Version from baseline to final visit were significantly improved for inattentive and combined subtype patients who received modafinil. Patients with the hyperactive-impulsive subtype who received modafinil demonstrated a greater mean improvement in ADHD-RS-IV School Version total score than did patients who received placebo, but the difference did not reach statistical significance (Figure 2). Mean changes in