Respiratory Medicine (2007) **101**, 616–627

ELSEVIER

respiratoryMEDICINE

Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome

M. Hirshkowitz[a,*], J.E. Black[b], K. Wesnes[c], G. Niebler[d], S. Arora[d], T. Roth[e]

[a]*Michael E. DeBakey VAMC Sleep Center, Baylor College of Medicine, Houston, TX 77030, USA*
[b]*Stanford University, Stanford, CA 94305, USA*
[c]*Cognitive Drug Research, Ltd, Goring-on-Thames, UK RG8 0EN*
[d]*Cephalon, Inc, Frazer, PA 19355, USA*
[e]*Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI 48202, USA*

Received 1 December 2005; accepted 9 June 2006

KEYWORDS
Armodafinil;
Obstructive sleep apnea/hypopnea syndrome;
Wakefulness;
Memory;
Fatigue;
Excessive sleepiness

Summary
Objective: Armodafinil is the *R*-enantiomer of racemic modafinil and has a significantly longer half-life than the *S*-enantiomer. This study evaluated armodafinil 150 mg/day as an adjunct treatment for residual excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome (OSA/HS) who were otherwise well controlled with nasal continuous positive airway pressure (nCPAP). We assessed the ability of armodafinil to improve wakefulness and cognition and reduce fatigue in this population.
Methods: In this 12-week, randomized, double-blind study, patients ($n = 259$) received armodafinil (150 mg) or placebo once daily. Efficacy assessments at baseline and weeks 4, 8, and 12 included the Maintenance of Wakefulness Test (MWT), Clinical Global Impression of Change (CGI-C), Cognitive Drug Research battery, Epworth Sleepiness Scale, and Brief Fatigue Inventory.
Results: At final visit, mean (SD) MWT sleep latency increased from baseline by 2.3 (7.8) min with armodafinil and decreased by 1.3 (7.1) min in the placebo group ($P = 0.0003$). Armodafinil improved clinical condition (CGI-C, 71% vs. 53% for armodafinil and placebo, respectively; $P = 0.0069$). Armodafinil significantly improved episodic secondary memory ($P = 0.0102$) and patient-estimated wakefulness ($P < 0.01$) and reduced fatigue ($P < 0.05$) compared with placebo. Armodafinil did not adversely affect nCPAP use. The most common adverse event associated with armodafinil was headache. Sleep macroarchitecture was not altered by armodafinil.
Conclusion: Adjunct treatment with armodafinil significantly improved alertness, overall clinical condition, and long-term memory. Armodafinil also reduced fatigue and the impact

*Corresponding author. Tel.: 713 794 7562; fax: 713 794 7558.
E-mail address: maxh@bcm.tmc.edu (M. Hirshkowitz).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2006.06.007

of sleepiness on daily activities in patients with OSA/HS who have residual excessive sleepiness notwithstanding regular use of nCPAP. Armodafinil was well tolerated.

Introduction

Obstructive sleep apnea/hypopnea syndrome (OSA/HS) afflicts 7–20% of American adults.[1] OSA/HS usually reduces an individual's overall functioning; is associated with excessive sleepiness (ES), fatigue, and lack of energy; and often adversely affects memory, concentration, and attention.[2,3] Nasal continuous positive airway pressure (nCPAP) is the standard of care for treating OSA/HS. It reduces sleepiness,[4,5] improves functioning,[6] and improves self-reported health status.[4,7] However, some patients who regularly use nCPAP experience residual ES.[8] Studies have shown that modafinil improves wakefulness in patients with OSA/HS who have residual ES notwithstanding adequate nCPAP use.[9,10] Modafinil is the only drug currently approved for the treatment of ES in this patient population.

Modafinil is a racemic compound containing equal amounts of *R*-modafinil and *S*-modafinil. The *R*-enantiomer, also known as armodafinil, has a half-life of 10–14 h compared with 3–4 h for that of the *S*-enantiomer.[11–13] Following chronic use of modafinil, the proportion of circulating *R*-modafinil can be as much as three times greater than that of circulating *S*-modafinil.[11–13] Therefore, most of the wakefulness maintenance effects of racemic modafinil could theoretically be attributable to armodafinil. This study assessed whether the therapeutically beneficial effects of racemic modafinil for improving wakefulness[9,10,14] could be replicated by administering armodafinil alone.

This randomized, double-blind, placebo-controlled study assessed the efficacy and tolerability of armodafinil 150 mg/day as adjunct therapy to nCPAP for improving wakefulness in patients with OSA/HS with residual ES notwithstanding regular and effective nCPAP therapy.

Methods

Patient selection

Eligible subjects included men and women, age 18–65 years, who were diagnosed with OSA/HS[15] and complained of residual ES notwithstanding effective, regular, and adequate use of nCPAP. The nCPAP criteria included stable therapy (for at least 4 weeks); effective therapy (an apnea-hypopnea index [AHI] $\leqslant$ 10 during overnight polysomnography); and regular and adequate nCPAP use ($\geqslant$ 4 h per night on at least 70% of the nights during a 2-week evaluation period). A Clinical Global Impression of Severity of illness[16] rating of $\geqslant$ 4 (corresponding to moderately ill or worse) and an Epworth Sleepiness Scale (ESS)[17] score of $\geqslant$ 10 were required. Female patients of childbearing potential were required to have a negative serum pregnancy test at screening and use a medically accepted method of birth control. Steroidal contraceptives had to be used in conjunction with a barrier method.

Individuals were excluded from the study if they had the following: any clinically significant, uncontrolled psychiatric or medical conditions that could account for their ES; a probable or confirmed diagnosis of another sleep disorder (other than OSA/HS); or any disorder that might interfere with drug absorption, distribution, metabolism, or excretion or produce daytime sleepiness. Other exclusion criteria included pregnancy or lactation; consumption of $>$ 600 mg/day of caffeine; history of alcohol or drug abuse[18]; medical requirement for drugs disallowed by the protocol (modafinil, melatonin, sodium oxybate, lithium, St. John's wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, monoamine oxidase inhibitors, anticoagulants, anticonvulsants, and barbiturates); use of clinically significant amounts of nonprescription drugs within 7 days of the screening visit; use of investigational drugs within 1 month of the screening visit; or clinically significant drug sensitivity to stimulants or modafinil. The study was conducted between March 26 and October 23, 2004.

Study design

This 12-week, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 36 centers in the United States, Australia, Russia, Germany, and France. The protocol was approved by an Independent Ethics Committee or an Institutional Review Board at each participating center. Furthermore, the study was conducted according to international, national, and local laws and regulations. Patients provided written informed consent. Screening assessments included a 2-week period of at-home nCPAP therapy using a REMstar Auto nCPAP System (Respironics, Murrysville, PA) to assess adherence and nighttime polysomnography to determine nCPAP effectiveness. The REMstar Auto nCPAP device was used in CPAP mode. Patients returned to the clinic for baseline assessments, randomization, and drug dispensation and for postbaseline assessments (weeks 4, 8, and 12) and nighttime polysomnography (week 12 only).

Patients meeting inclusion, exclusion, and screening criteria were randomized (1:1) via an interactive voice randomization system to receive armodafinil 150 mg, formulated as film-coated 50-mg tablets, or a matching placebo. Because of the large number of planned centers, randomization was stratified by country. Patients assigned to armodafinil received 50 mg on the first day followed by an additional 50 mg/day for two consecutive days, with the final dosage reached on day 4. Patients assigned to placebo were titrated in the same manner. Study drug was packaged in child-resistant blister cards. At home, patients took study drug once daily in the morning before 0800 h, approximately 30 min before breakfast. On clinic days, study drug was taken at approximately 0700 h. Patients and investigators