ORIGINAL ARTICLE

Armodafinil improves wakefulness and long-term episodic memory in nCPAP-adherent patients with excessive sleepiness associated with obstructive sleep apnea

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Abstract Residual excessive sleepiness (ES) and impaired cognition can occur despite effective and regular nasal continuous positive airway pressure (nCPAP) therapy in some patients with obstructive sleep apnea (OSA). A pooled analysis of two 12-week, randomized, double-blind studies in nCPAP-adherent patients with ES associated with OSA evaluated the effect of armodafinil on wakefulness and cognition. Three hundred and ninety-one patients received armodafinil (150 or 250 mg) and 260 patients received placebo once daily for 12 weeks. Efficacy assessments included the Maintenance of Wakefulness Test (MWT), Cognitive Drug Research cognitive performance battery, Epworth Sleepiness Scale, and Brief Fatigue Inventory. Adverse events were monitored. Armodafinil increased mean MWT sleep latency from baseline to final visit by 2.0 min vs a decrease of 1.5 min with placebo ($P < 0.0001$). Compared with placebo, armodafinil significantly improved quality of episodic secondary memory ($P < 0.05$) and patients' ability to engage in activities of daily living ($P < 0.0001$) and reduced fatigue ($P < 0.01$). The most common adverse events were headache, nausea, and insomnia. Armodafinil did not adversely affect desired nighttime sleep, and nCPAP use remained high (approximately 7 h/night). Adjunct treatment with armodafinil significantly improved wakefulness, long-term memory, and patients' ability to engage in activities of daily living in nCPAP-adherent individuals with ES associated with OSA. Armodafinil also reduced patient-reported fatigue and was well tolerated.

Keywords Armodafinil · Fatigue · Obstructive sleep apnea syndrome · Sleepiness · Wakefulness

Introduction

Obstructive sleep apnea (OSA) syndrome includes excessive sleepiness (ES), fatigue, sleep fragmentation, impaired alertness, cognitive dysfunction, and mood disturbances [1, 2]. OSA is typically characterized by recurrent complete or partial airway collapse during sleep, resulting in frequent apnea and hypopneic events lasting at least 10 s [1]. Although the reported prevalence of OSA in the general population varies as a function of diagnostic criteria [2], OSA syndrome has been estimated to occur in 4 and 2% of middle-aged North American men and women, respectively [3]. OSA can lead to serious medical, social, and public safety consequences, and patients are at an increased risk for cardiovascular disease [4] and motor vehicle and occupational accidents [5, 6]. Quality of life and social functioning are also significantly impaired in this patient population [7, 8]. Fatigue, in particular, can contribute to reduced quality of life [1, 9]; thus, the assessment of patient-rated fatigue is an important outcome to evaluate and monitor in patients with OSA.

Nasal continuous positive airway pressure (nCPAP) therapy is the recommended standard of care for treating patients with moderate to severe OSA [10]. In a comprehensive review of 36 clinical studies, nCPAP therapy was shown to effectively reduce objective and subjective

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measures of sleepiness and improve quality of life in patients with moderate and severe OSA [11]. However, despite receiving adequate nCPAP therapy, half of patients with OSA still experience residual ES as measured by objective assessments as well as impairments in mood or cognition [12–18]. Cognitive impairment in patients with OSA is characterized by deficits in attention, learning and memory, and executive function (planning and problem solving) and may persist despite nCPAP therapy [12, 15–17]. A review of the literature suggests that while nCPAP therapy can substantially improve quality of life for patients with OSA, it has a smaller effect on improving cognitive performance [7].

Modafinil, a racemic mixture consisting of equal amounts of *R*- and *S*-enantiomers, has been shown to improve wakefulness in patients with OSA who experience residual ES despite regular nCPAP use [19, 20]. Pharmacokinetic studies have shown that the half-life of *R*-modafinil (10–14 h) is significantly longer than the half-life of *S*-modafinil (3–4 h) [21–23]. Armodafinil has higher plasma concentrations later in the day compared to modafinil on a "milligram-to-milligram" basis and improves healthy subjects' wakefulness and ability to sustain attention for a longer period of time compared with modafinil [24]. Armodafinil has also recently been shown to improve wakefulness in patients with ES associated with narcolepsy in a 12-week double-blind, placebo-controlled study [25].

Recent findings from two 12-week, double-blind, placebo-controlled studies of similar design indicate that armodafinil improved wakefulness and overall clinical condition in nCPAP-adherent patients with OSA and residual ES [26, 27]. In the present pooled analysis of the two OSA studies [26, 27], the effects on wakefulness, cognition, and fatigue and the safety and tolerability of armodafinil compared with placebo were evaluated in OSA patients adherent to nCPAP therapy.

Materials and methods

Study design and procedures

Data from two 12-week, multicenter, double-blind, placebo-controlled, parallel-group clinical studies were pooled for analysis. The pooling of these data was based on similarities in patient population, study design, and treatment duration in the two studies [26, 27]. One study was conducted in 36 centers across the USA, Australia, Russia, Germany, and France [26], and the other study was conducted in 37 centers across the USA and Canada [27]. The study protocols were approved by an Independent Ethics Committee or Institutional Review Board at each center. Both studies were conducted in accordance with the Good

Clinical Practice: Consolidated Guideline [28] and national and local laws and regulations.

Patients were randomized to receive armodafinil 150 mg (*n*=129) or placebo (*n*=130) daily in the first study [26] and armodafinil 150 (*n*=131) or 250 mg/day (*n*=131), or placebo (*n*=130) in the second study [27]. Study drugs were initiated with a dose of 50 mg/day on day 1 and then increased in increments of 50 mg starting on day 2 and every 2 days thereafter until the assigned dose was reached (i.e., 150 mg/day on day 4 for both studies or 250 mg/day on day 8 for the second study). The study drugs were taken once daily in the morning (before 08:00 and approximately 30 min before breakfast). Monitoring of patients' compliance with study drug administration was the responsibility of the investigator at each center and was assessed by completed study drug accountability records and reviews of patient diaries. nCPAP use at home was also monitored objectively by investigators at each visit to the study center, using the REMstar® Auto CPAP System (Respironics, Murrysville, PA). The REMstar Auto CPAP System was used in CPAP mode.

Patient selection criteria

Methods for selecting patients in both studies have been described previously [26, 27]. Men and women 18 to 65 years of age with a current diagnosis of OSA as defined by the *International Classification of Sleep Disorders* [1] were included in both studies. Patients were at least moderately ill (Clinical Global Impression of Severity of Illness rating greater than or equal to 4) [29] and had a complaint of ES. Patients were eligible if ES was determined to be pathological, based on an Epworth Sleepiness Scale (ESS) score greater than or equal to 10 [30]. All patients were receiving stable (greater than or equal to 4 weeks) and effective nCPAP therapy on a regular basis (greater than or equal to 4 h per night on greater than or equal to 70% of nights) during the 2-week evaluation period. The CPAP use was monitored using the REMstar Auto CPAP System. Effectiveness of therapy was determined by an apnea–hypopnea index (AHI) less than or equal to ten events per hour on nighttime polysomnography (PSG).

Patient exclusion criteria

Patients were excluded if they had any of the following: a diagnosis of a sleep disorder other than OSA, symptoms of ES associated with a clinically significant uncontrolled medical or psychiatric condition as determined by the investigator, any disorder that might interfere with drug absorption, distribution, metabolism, or excretion, a history of drug or alcohol abuse, as determined by the Diagnostic

and Statistical Manual of Mental Disorders IV criteria [31] or by a positive result from the urine drug screen given at screening and again at the final visit, caffeine consumption greater than 600 mg/day, or a clinically significant sensitivity to central nervous system stimulants or modafinil. Women who were pregnant or breast feeding were also excluded. The use of any substance that could affect wakefulness or sleepiness (e.g., modafinil, sodium oxybate, melatonin, lithium, St. John's wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, anticonvulsants, or barbiturates), use of other excluded agents (e.g., monoamine oxidase inhibitors, anticoagulants), use of clinically significant amounts of nonprescription drugs within 7 days of screening, and use of investigational drugs within 1 month of screening was prohibited. All patients provided written informed consent before participation in these studies and were compensated for their participation.

Assessments

Efficacy assessments

Efficacy assessments were performed for both studies at baseline and weeks 4, 8, and 12. The primary efficacy variables in the two individual studies were the change from baseline to final visit (week 12 or last postbaseline measurement) in mean Maintenance of Wakefulness Test (MWT) [32, 33] sleep latency averaged across the first four tests and the proportion of patients with at least minimal improvement on the Clinical Global Impression of Change (CGI-C) [29]. The MWT was conducted as six separate 30-min sessions at 09:00, 11:00, 13:00, 15:00, 17:00, and 19:00. Sleep latency was defined as the time to onset of the first of three consecutive epochs of stage 1 sleep or the time to onset of any epoch of stages 2, 3, and 4 sleep or rapid eye movement sleep [34]. Sleep latencies were averaged across the first four tests (09:00, 11:00, 13:00, 15:00) and the last three tests (15:00, 17:00, 19:00) to distinguish between early- and late-day effects, respectively. The proportion of patients with at least a minimal improvement on the CGI-C was assessed to determine patients' overall clinical improvement in the individual studies; however, these data were not poolable for this analysis because of a substantial difference in the percentage of responders to placebo between the two studies.

The Cognitive Drug Research (CDR) battery of tests [35, 36] was administered by computer as six separate 25-min sessions conducted at 09:30, 11:30, 13:30, 15:30, 17:30, and 19:30. The CDR battery includes five memory tests (immediate word recall, delayed word recall, numeric working memory, word recognition, and picture recognition) and three attention tests (simple reaction time, choice

reaction time, and digit vigilance). Two composite factors are derived from the memory tests in the CDR: quality of episodic secondary memory, a measure of long-term memory that measures the ability to recall verbal and visual information, and speed of memory, which assesses the time it takes to decide whether information is held in memory. Two composite factors are derived from the CDR for attention: power of attention, which measures the ability to focus attention and avoid distraction (concentration), and continuity of attention, which measures the ability to sustain attention (vigilance). Similar to the MWT, the CDR scores were averaged across the first four test sessions (09:30, 11:30, 13:30, 15:30) and the last three test sessions (15:30, 17:30, 19:30) to assess cognitive effects on early- and late-day measurements.

The patients' ability to engage in daily activities was assessed at each visit by the ESS [30]. ESS total scores range from 0 to 24, with higher scores indicating greater sleepiness. An ESS score greater than or equal to 10 indicates pathological sleepiness [30]. The severity and impact of patient-rated fatigue on daily functioning were assessed at each visit by the nine-item Brief Fatigue Inventory (BFI) [37] and were based on changes in global fatigue (average of all nine questions) and worst fatigue in the past 24 h (item 3). The rating scale for the BFI ranges from 0 (no fatigue) to 10 (as bad as you can imagine). A score of greater than or equal to 7 for either global fatigue or worst fatigue in the past 24 h is indicative of severe fatigue. Both the ESS and BFI were administered before the first MWT session (09:00) at each visit.

Safety and tolerability assessments

Adverse events were monitored and recorded by the study investigators at each center throughout both studies. Clinical laboratory tests (blood chemistry, hematology, urinalysis), vital signs (resting heart rate and systolic and diastolic blood pressure 3 and 13 h postadministration), and electrocardiograms were obtained at screening, baseline, and weeks 4, 8, and 12. Physical examinations were performed at baseline and week 12. Patients' use of nCPAP was monitored at least 2 weeks before baseline and throughout both studies using the Respironics REMstar Auto CPAP system. Effect on nighttime sleep was determined by PSG, which was performed the night immediately after the measurement of daytime MWT during the second screening visit and the final visit. The PSG was conducted for 8 h, starting within 30 min of the patient's usual bedtime but not earlier than 21:30.

Clinically significant elevations in resting systolic and diastolic blood pressure were defined a priori as greater than or equal to 140 mmHg with an increase of greater than or equal to 10% and greater than or equal to 90 mmHg with

an increase of greater than or equal to 10%, respectively. Patients with worsening hypertension included those who had a history of hypertension at baseline and who started new antihypertensive medication and/or increased the dose of previously used antihypertensive medication during the studies. Patients with newly diagnosed hypertension included those who had no history of hypertension at baseline and who started antihypertensive medication during the studies. Patients at risk for hypertension included those who had at least two clinically significant elevations in blood pressure readings between baseline and final visit.

Statistical analysis

Descriptive statistics were used to summarize continuous and categorical demographic variables. Efficacy assessments were analyzed at weeks 4, 8, and 12 using observed cases and at final visit (week 12 or last postbaseline measurement) using the last observation carried forward approach. Efficacy analyses included randomized patients who received at least one dose of study drug and had a baseline measurement with at least one postbaseline measurement on the MWT and CGI-C. Safety and tolerability analyses included all randomized patients who received at least one dose of study drug. All efficacy assessments were analyzed by analysis of variance (ANOVA) with treatment and study as factors. Tests of poolability for all continuous efficacy variables across the two studies were conducted using an ANOVA with treatment and study and treatment by study interaction as

factors. Vital signs and data from nighttime PSG were analyzed by Wilcoxon rank-sum test. For nCPAP use, the change from baseline to on-treatment values was analyzed using one-way ANOVA. All statistical tests were two-tailed, and the 5% level of significance was used.

Results

Patient demographics and disease characteristics

Of 658 patients randomized, 651 were included in the safety analysis, and 601 were evaluable for efficacy (Fig. 1). Patient demographics and disease characteristics for all patients in the safety analyses are summarized in Table 1. The mean body mass index was 36.6 kg/m^2. Patients reported high nightly nCPAP usage (mean [SD] hours of nightly use, armodafinil 6.9 [1.2] h; placebo 6.9 [1.0] h). The nCPAP therapy was effective, as shown by mean (SD) AHI values of 1.5 (3.3) and 1.2 (2.1) events/h in the armodafinil and placebo groups, respectively. Overall, 41% of patients had a history of hypertension at baseline.

Effects on wakefulness

Mean (SD) sleep latency at baseline across the first four MWTs (09:00, 11:00, 13:00, 15:00) was 22.8 (8.4) and 23.2 (7.9) min for the armodafinil and placebo groups, respectively. At all study visits, armodafinil significantly improved mean sleep latency across the first four MWTs
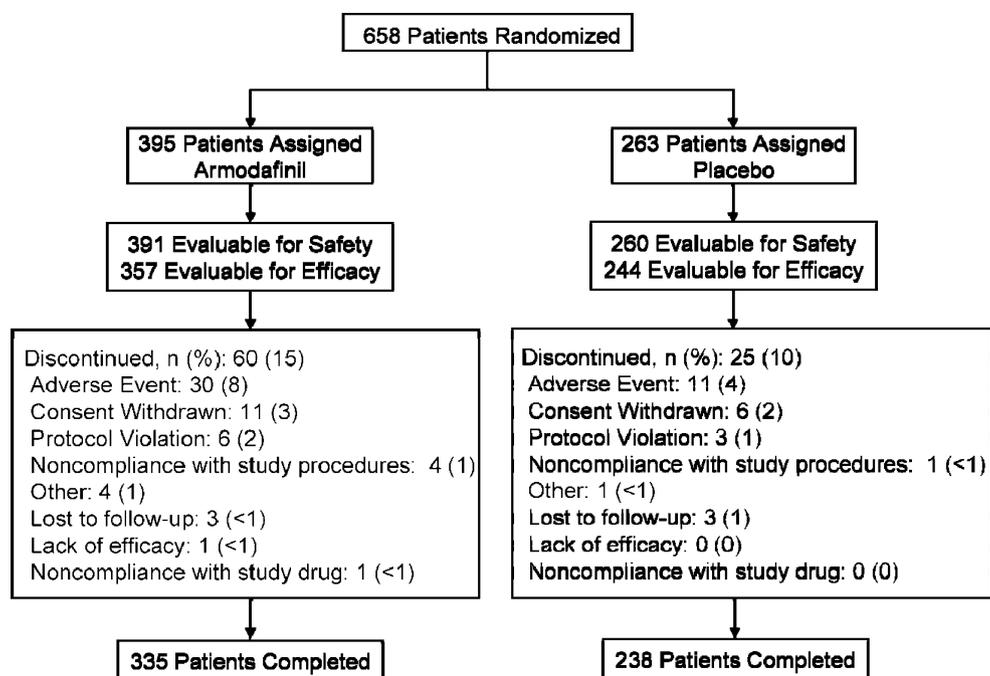
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                      ┌──────────────────────────┐
                      │  658 Patients Randomized  │
                      └──────────────────────────┘
                    ┌───────────────┴───────────────┐
        ┌──────────────────────┐          ┌──────────────────────┐
        │ 395 Patients Assigned│          │ 263 Patients Assigned│
        │     Armodafinil      │          │       Placebo        │
        └──────────────────────┘          └──────────────────────┘
        ┌──────────────────────┐          ┌──────────────────────┐
        │391 Evaluable for     │          │260 Evaluable for     │
        │      Safety          │          │      Safety          │
        │357 Evaluable for     │          │244 Evaluable for     │
        │      Efficacy        │          │      Efficacy        │
        └──────────────────────┘          └──────────────────────┘
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Discontinued, n (%): 60 (15)
Adverse Event: 30 (8)
Consent Withdrawn: 11 (3)
Protocol Violation: 6 (2)
Noncompliance with study procedures: 4 (1)
Other: 4 (1)
Lost to follow-up: 3 (<1)
Lack of efficacy: 1 (<1)
Noncompliance with study drug: 1 (<1)

Discontinued, n (%): 25 (10)
Adverse Event: 11 (4)
Consent Withdrawn: 6 (2)
Protocol Violation: 3 (1)
Noncompliance with study procedures: 1 (<1)
Other: 1 (<1)
Lost to follow-up: 3 (1)
Lack of efficacy: 0 (0)
Noncompliance with study drug: 0 (0)

335 Patients Completed   238 Patients Completed

Fig. 1 Patient disposition

Table 1 Patient demographics and baseline characteristics

Characteristic	Armodafinil (n=391)	Placebo (n=260)
Age (years)		
Mean (SD)	49.7 (9.0)	50.3 (9.1)
Sex, n (%)		
Men	283 (72)	183 (70)
Women	108 (28)	77 (30)
Race, n (%)		
White	327 (84)	224 (86)
Black	36 (9)	21 (8)
Asian	6 (2)	3 (1)
Other	22 (6)	11 (4)
Missing	0	1 (<1)
Weight (kg)		
Mean (SD)	110.4 (24.6)	111.2 (23.7)
BMI (kg/m^2)		
Mean (SD)	36.4 (8.0)	36.9 (7.5)
CGI-S, n (%)		
Moderately ill	219 (56)	138 (53)
Markedly, severely, or extremely ill	172 (44)	122 (47)
nCPAP (h)		
Mean (SD)	6.9 (1.2)	6.9 (1.0)
AHI		
Mean (SD)	1.5 (3.3)	1.2 (2.1)
History of hypertension		
n (%)	159 (41)	108 (42)

AHI Apnea–hypopnea index, *BMI* body mass index, *CGI-S* Clinical Global Impression of Severity of Illness, *nCPAP* nasal continuous positive airway pressure

compared with placebo (Fig. 2a). The mean change from baseline in sleep latency at final visit was 2.0 min for the armodafinil group compared with −1.5 min for the placebo group ($P<0.0001$).

Armodafinil also improved patients' ability to maintain late-day wakefulness (MWTs at 15:00, 17:00, 19:00) compared with placebo (Fig. 2b). Mean (SD) sleep latency at baseline across the last three MWTs was 24.4 (7.8) and 24.6 (7.4) min for the armodafinil and placebo groups, respectively. The mean change from baseline in sleep latency at final visit was 1.1 min for the armodafinil group compared with −0.3 min for the placebo group ($P<0.05$).

Effects on memory and attention

Compared with placebo, armodafinil significantly improved the quality of episodic secondary memory across the first four tests (09:30, 11:30, 13:30, 15:30) at all study visits ($P<0.05$; Fig. 3a). The mean (SD) change from baseline in quality of episodic secondary memory at final visit was 10.2 (31.7) U for the armodafinil group compared with −0.7 (46.3) U for the placebo group ($P<0.01$). Differences between the treatment groups did not achieve statistical significance at

the final visit for speed of memory, power of attention, or continuity of attention across the first four tests.

Across the later three tests of the day (15:30, 17:30, 19:30), the difference in the quality of episodic secondary memory was statistically significant at week 8 for armodafinil compared with placebo ($P=0.011$; Fig. 3b), with a trend toward significance at week 12 ($P=0.081$). The difference between treatment groups was not statistically significant at the final visit for the quality of episodic secondary memory. There were no significant changes from baseline to final visit between the armodafinil and placebo groups for speed of memory, power of attention, or continuity of attention across the last three tests.

Effects on patients' ability to engage in activities

The mean (SD) ESS scores were high at baseline (15.4 [3.5] and 15.9 [3.5] for the armodafinil and placebo groups, respectively), despite the high nCPAP use as shown in Table 1. Compared with placebo, treatment with armodafinil significantly improved patients' ability to engage in activities of daily living (ESS) at all visits ($P<0.0001$; Fig. 4). Nearly half of all patients (49%) in the armodafinil group responded to treatment (total ESS score less than 10 at final visit) compared with 26% in the placebo group.
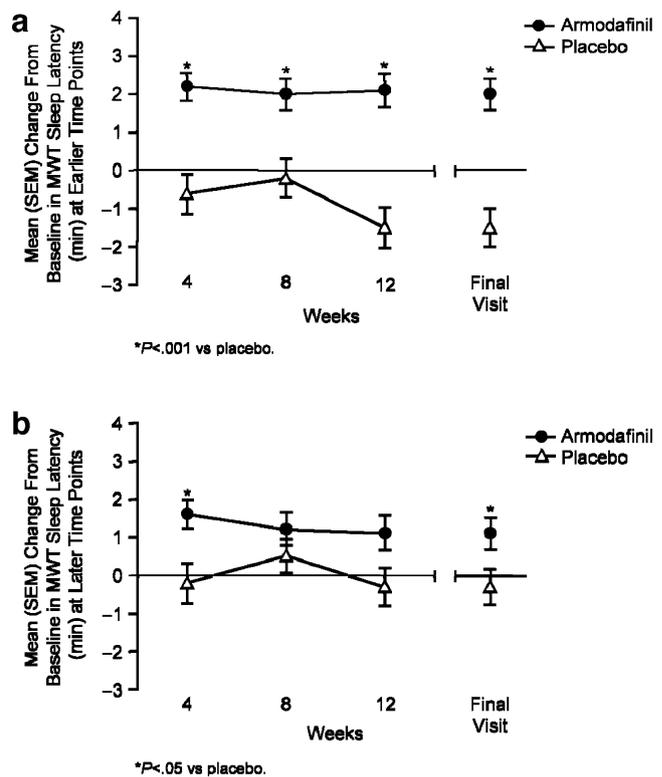

Fig. 2 Mean (SEM) change from baseline in sleep latency from the Maintenance of Wakefulness Test (MWT). **a** Sleep latencies averaged across the first four tests (09:00–15:00). **b** Sleep latencies averaged across the last three tests (15:00–19:00)
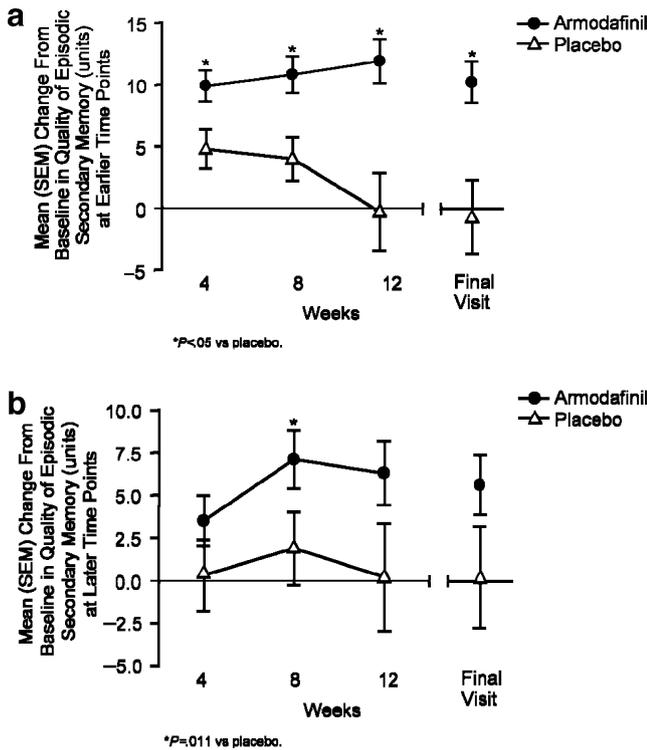
Fig. 3 Mean (SEM) change from baseline in quality of episodic secondary memory. **a** Scores averaged across the first four tests (09:30–15:30). **b** Scores averaged across last three tests (15:30–19:30)
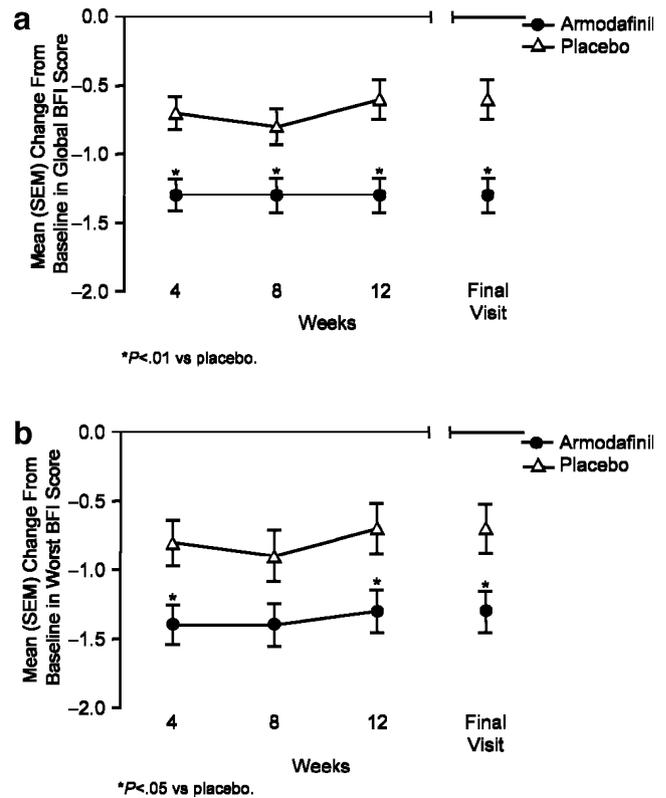

Fig. 5 Mean (SEM) change from baseline in fatigue. **a** Global fatigue. **b** Worst fatigue in the past 24 h. *BFI* Brief Fatigue Inventory

Effects on fatigue

The mean (SD) scores for global fatigue from the BFI at baseline were 4.8 (1.9) and 4.9 (1.9) for the armodafinil and placebo groups, respectively. Armodafinil significantly improved global fatigue at all visits compared with placebo ($P<0.01$; Fig. 5a). Mean scores for worst fatigue in the past 24 h from the BFI at baseline were nearly identical for the armodafinil and placebo groups (7.2 [2.0] and 7.3 [2.0], respectively) and indicated severe fatigue (score greater than or equal to 7). Armodafinil significantly improved

scores for worst fatigue in the past 24 h at weeks 4 and 12 and at the final visit ($P<0.05$ vs placebo; Fig. 5b), with a trend toward significance at week 8 ($P=0.056$ vs placebo).

Safety and tolerability

Armodafinil was well tolerated, with a low incidence of adverse events, most of which were mild to moderate in nature. Headache was the most commonly reported adverse event, defined as occurring in greater than or equal to 5% in either group (Table 2). Serious adverse events were considered by the investigator unlikely to be or not related to armodafinil (ulcerative colitis, $n=1$; migraine, $n=1$; worsening of Axis II disorder and mood disorder, $n=1$; duodenal ulcer hemorrhage, $n=1$). One serious adverse event was reported in the placebo group (gastroesophageal reflux disease). The most frequently occurring adverse

Fig. 4 Mean (SEM) change from baseline in Epworth Sleepiness Scale total score

Table 2 Adverse events occurring in ≥5% of patients

Adverse event, n (%)	Armodafinil ($n=391$)	Placebo ($n=260$)
Headache	65 (17)	20 (8)
Nausea	22 (6)	10 (4)
Insomnia	22 (6)	3 (1)
Dizziness	19 (5)	4 (2)
Anxiety	20 (5)	2 (<1)

events that led to discontinuation among patients receiving armodafinil were headache ($n=5$) and nausea ($n=4$).

There were no clinically significant changes from baseline to final visit in either the armodafinil group or the placebo group for laboratory values, electrocardiogram parameters, or physical examinations. There were also no meaningful changes (clinical or statistical) from baseline to final visit for systolic blood pressure (0.2 [14.2] mmHg for armodafinil vs −1.0 [14.6] mmHg for placebo), diastolic blood pressure (0.3 [9.3] mmHg for armodafinil vs −1.0 [10.0] mmHg for placebo), and heart rate (2.3 [9.6] bpm for armodafinil vs 1.4 [9.6] bpm for placebo).

The incidence of patients with newly diagnosed hypertension was less than 1% in the armodafinil group and less than 1% in the placebo group. The proportion of patients at risk for hypertension was similar for both treatment groups (18% of 391 patients, armodafinil group; 16% of 260 patients, placebo group). The incidence of patients with worsening hypertension was 3% of 391 patients in the armodafinil group and 2% of 260 patients in the placebo group.

nCPAP use remained high (approximately 7 h/night) throughout both of the studies. The duration of nCPAP use at final visit was reduced from baseline by a mean (SD) of −0.3 (0.7) h with armodafinil compared with −0.1 (0.6) h with placebo (a between-group difference of about 12 min; $P<0.0001$). At final visit, AHI values remained low and were comparable between the armodafinil and placebo groups ($P>0.05$ vs placebo). In addition, there were no significant changes from baseline in nocturnal PSG sleep variables between the armodafinil and placebo groups ($P>0.05$; Table 3).

Discussion

Recognizing and effectively managing ES in patients with OSA is essential for clinicians because of the profound impact that ES has on the patients, their families and coworkers, and the general public (e.g., increased risk of traffic accidents) [4–6]. Without appropriate treatment, ES adversely affects cognitive [15, 17], occupational [6], and social functioning [8]. Several studies evaluated in a comprehensive review [11] have shown that there is general improvement in wakefulness with nCPAP therapy, especially in patients with more severe OSA. Nonetheless, residual ES can persist even after effective nCPAP treatment [18], suggesting that there is need for adjunctive therapy to treat ES in these patients.

The present study re-evaluates the findings from two separate studies on the effects of armodafinil in patients with refractory ES associated with OSA and provides additional information regarding secondary analyses, for which the individual studies may not have had adequate statistical power. In the individual studies [26, 27], armodafinil was shown to significantly improve daytime mean sleep latency across the first four tests on the MWT and overall clinical condition as assessed by the CGI-C. In the pooled analysis, armodafinil significantly improved patients' ability to sustain wakefulness as objectively assessed by the MWT. Improvements in mean sleep latency were observed at the first visit at week 4 and were maintained throughout the remainder of the study. The lack of a consistent effect of armodafinil on wakefulness across the last three MWTs (15:00, 17:00, 19:00) likely reflects the high mean sleep latency (approximately 24.5 min) at these times. Behavioral effects, causing poorer performance on the last test of the day, and high intertest variability in sleep latency may have also contributed to this finding [38].

The individual studies also included the clinician's subjective assessment of treatment effect on ES, the CGI-C. Data for the CGI-C, however, were not poolable for this analysis because of substantial differences in the proportion of patients considered responders to placebo between the two studies. In the individual studies, the proportion of patients considered

Table 3 Nocturnal polysomnography parameters[a]

Variable (units), mean (SD)	Armodafinil ($n=391$)		Placebo ($n=260$)	
	Baseline	Final Visit	Baseline	Final Visit
Latency to persistent sleep (min)	22.3 (26.9)	19.6 (20.5)	21.3 (24.0)	20.8 (21.4)
Number of arousals, n	20.0 (11.3)	18.5 (10.2)	18.7 (9.7)	18.4 (10.4)
Number of awakenings, n	8.8 (4.7)	9.2 (5.3)	8.7 (5.1)	9.6 (5.4)
Sleep efficiency (%)	82.4 (10.9)	82.0 (12.0)	82.0 (12.1)	81.4 (11.2)
Wake after sleep onset (min)	66.6 (43.9)	69.1 (48.5)	68.7 (50.3)	70.2 (46.5)
Stage 1 (%)	11.2 (6.4)	10.5 (5.5)	10.9 (6.1)	10.6 (6.2)
Stage 2 (%)	59.3 (9.8)	58.8 (11.2)	58.8 (10.1)	57.7 (11.2)
Stage 3/4 (%)	10.6 (9.0)	10.3 (9.0)	10.8 (9.6)	10.9 (10.2)
REM (%)	18.9 (6.9)	19.8 (7.1)	19.5 (7.2)	20.7 (8.0)

REM Rapid eye movement
[a] No significant differences between baseline and final visit were observed.

responders to armodafinil and placebo was 71 and 53%, respectively, in one study [26] and 72 and 37%, respectively, in the other study [27].

Cognitive impairment is common in patients with OSA [17]. Although the etiology has not been definitively determined, decreased cortical activity because of impaired arousal or neuronal damage because of chronic intermittent hypoxia are possible causes [16, 39–41]. It is not yet clear what additional interventions may be effective in restoring cognitive function in patients with OSA. Findings from studies evaluating the effects of nCPAP therapy on memory and attention have yielded inconsistent results [15, 16, 40, 42, 43]. Unlike the findings from the individual armodafinil OSA studies [26, 27], the pooled analysis showed that adjunct armodafinil significantly improves long-term memory (i.e., quality of episodic secondary memory) at all study visits compared with placebo, indicating that treatment was associated with a greater ability to recall verbal and visual information. Interestingly, the long-term memory benefit occurred independent of a consistent benefit on attention and concentration. It is important to note that the CDR composite factors in both of the individual armodafinil OSA studies were secondary efficacy variables. Thus, although results from the pooled analysis provide a more precise estimate of the effects on long-term memory, further studies are needed to determine the potential role of armodafinil in improving cognitive function in nCPAP-adherent patients with OSA and associated ES.

Armodafinil significantly improved patients' ability to engage in activities of daily living at all visits as measured by the ESS. The patient population studied in this pooled analysis had severe ES (mean ESS score greater than 15) despite effective and regular nCPAP therapy. At the final visit, 49 and 26% of patients receiving armodafinil and placebo, respectively, had ESS scores less than 10, indicating that nearly half of patients no longer had pathological sleepiness with adjunct armodafinil treatment.

Fatigue may be the presenting complaint of patients with ES [44] and is a common associated symptom [45, 46]. Armodafinil significantly reduced fatigue, a result similar to findings from the individual studies [26, 27]. Armodafinil reduced global fatigue from a baseline value of 4.8 to a final visit value of 3.6. Similarly, worst fatigue in the past 24 h was reduced from a baseline of 7.2 to 5.8 at final visit. These findings indicate that armodafinil significantly reduced the severity of global fatigue and worst fatigue in the past 24 h to the mild-to-moderate range of fatigue (BFI score less than 7 [37]).

This pooled analysis shows that armodafinil does not adversely affect nighttime sleep in patients with OSA even with its longer-lasting duration of action compared with modafinil on a milligram-to-milligram basis [24]. Armodafinil was well tolerated; in general, adverse events were rated as mild to moderate in nature, although some patients discontinued because of adverse events. There were some minor changes in vital signs; however, these effects were not considered to be clinically significant. The patient population selected for both studies was verified to be adherent to nCPAP therapy; thus, the primary pathology of OSA was being treated in an appropriate and effective manner throughout the course of the two studies. At the final visit, the duration of nCPAP use had decreased minimally from baseline compared with placebo. Average nCPAP use remained high (approximately 7 h/night) and was effective (i.e., low AHI values). Adjunct armodafinil treatment did not affect arousals.

Findings from the present pooled analysis are limited to patients with OSA who have residual ES despite regular and effective nCPAP therapy and should not be generalized to patients with OSA who are not receiving adequate nCPAP therapy or are not using it regularly. Additionally, the 12-week duration of treatment in these studies limits the applicability of observed results to a longer period of treatment. It should be recognized that armodafinil does not treat the underlying airway obstruction and should not be considered a replacement for nCPAP therapy in patients with OSA. Further research is needed to determine the role armodafinil may have in improving cognitive function and whether the significant reduction in fatigue observed in the pooled analysis will contribute toward improved quality of life in this patient population.

In conclusion, pooled data from two 12-week, double-blind, placebo-controlled studies showed that once-daily administration of armodafinil significantly improved wakefulness when used as adjunct therapy in nCPAP-adherent patients with residual ES associated with OSA. The effect on wakefulness with armodafinil was maintained throughout the day. Importantly, adjunctive treatment with armodafinil was associated with significant improvements in long-term memory and patients' ability to engage in daily activities. Armodafinil significantly reduced fatigue in the studied population and was well tolerated.

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