NEW RESEARCH

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Effect of Armodafinil on Cortical Activity and Working Memory in Patients with Residual Excessive Sleepiness Associated with CPAP-Treated OSA: A Multicenter fMRI Study

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SCIENTIFIC INVESTIGATIONS

Study Objective: To assess the effect of armodafinil on task-related prefrontal cortex activation using functional magnetic resonance imaging (fMRI) in patients with obstructive sleep apnea (OSA) and excessive sleepiness despite continuous positive airway pressure (CPAP) therapy.

Methods: This 2-week, multicenter, prospective, randomized, double-blind, placebo-controlled, parallel-group study was conducted at five neuroimaging sites and four collaborating clinical study centers in the United States. Patients were 40 right-handed or ambidextrous men and women aged between 18 and 60 years, with OSA and persistent sleepiness, as determined by multiple sleep latency and Epworth Sleepiness Scale scores, despite effective, stable use of CPAP. Treatment was randomized (1:1) to once-daily armodafinil 200 mg or placebo. The primary efficacy outcome was a change from baseline at week 2 in the volume of activation meeting the predefined threshold in the dorsolateral prefrontal cortex during a 2-back working memory task. The key secondary measure was the change in task response latency.

Results: No significant differences were observed between treatment groups in the primary or key secondary outcomes. Armodafinil was generally well tolerated. The most common adverse events (occurring in more than one patient [5%]) were headache (19%), nasopharyngitis (14%), and diarrhea (10%).

Conclusions: Armodafinil did not improve fMRI-measured functional brain activation in CPAP-treated patients with OSA and excessive sleepiness.

Keywords: Armodafinil, cortical activation, excessive sleepiness, functional magnetic resonance imaging, neuroimaging, obstructive sleep apnea, 2-back task

Study Registration: Double-Blind, Placebo-Controlled, Functional Neuroimaging Study of Armodafinil (200 mg/Day) on Prefrontal Cortical Activation in Patients With Residual Excessive Sleepiness Associated With Obstructive Sleep Apnea/Hypopnea. ClinicalTrials.gov Identifier: NCT00711516. http://www.clinicaltrials.gov/ct2/show/study/NCT00711516

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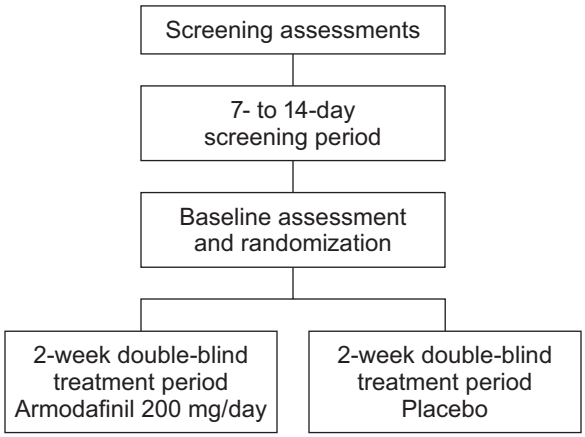
Impaired attention/vigilance, executive function, and mood are features of obstructive sleep apnea (OSA), a condition associated with excessive sleepiness, loss of sleep time, sleep fragmentation, intermittent nocturnal hypoxia, blood pressure non-dipping, and impaired cytokine/metabolic regulation.[1-5] Continuous positive airway pressure (CPAP) is effective treatment, yet a significant minority of patients experience persistent sleepiness or cognitive impairment.[6,7] While inadequate use, complex sleep apnea, technical factors such as mask leak, and comorbid illnesses such as depression and circadian phase delay may explain some of the residual symptoms, poor recovery of brain function despite excellent treatment compliance is a well-recognized clinical outcome.[7,8] Impaired recovery could reflect effects of true brain injury that are not reversible.[8-12]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Impaired attention/vigilance, executive function, and mood are features of obstructive sleep apnea (OSA), and a vulnerability of the prefrontal cortex has been consistently demonstrated. The purpose of this study was to assess the effect of armodafinil on task-related prefrontal cortex activation using functional magnetic resonance imaging (fMRI) in patients with OSA and excessive sleepiness despite continuous positive airway pressure (CPAP) therapy.

Study Impact: Armodafinil has consistently been shown to reduce subjective and objective sleepiness in patients with narcolepsy, sleep apnea, shift work sleep disorder, and jet lag, yet effects on brain activation have not been previously described. The findings of a non-response to armodafinil treatment may support the hypothesis that the brain in those with persistent sleepiness despite good sleep apnea treatment shows features of permanent injury and impaired neurocircuitry. Further investigation into this possibility is warranted.

Figure 1—Study design.



Stimulant and wakefulness-promoting medications have been used with some success in patients with residual sleepiness following sleep apnea treatment. Besides self-treatment with caffeine-containing beverages, these treatments include the amphetamines and their derivatives, as well as modafinil and armodafinil.[13-17] The brain mechanisms mediating known positive treatment effects are not well understood, but likely involve at least enhancement of dopaminergic systems.[18,19] The neuroanatomical substrates and/or functional network correlates underlying the effects of such interventions are not known.

Sleep apnea is associated with altered activation in task-specific neural networks as assessed by functional magnetic resonance imaging (fMRI), with most but not all reports suggesting a reduced activation.[20-22] While different investigators have used different imaging protocols, the majority have used verbal working memory tasks, and a vulnerability of the prefrontal cortex has been consistently demonstrated.[20] The reversibility of anatomical or functional changes with treatment is being demonstrated,[23,24] but the reversibility may not be complete. Thus, imaging biomarkers that focus on the prefrontal cortex seem reasonable choices for assessing sleep apnea related pathology and the impact of therapies.

Stimulants have complex effects on activation in relation to task difficulty and sleep deprivation. For example, modafinil has been associated with preservation of cortical and subcortical activation following sleep deprivation,[25] with the greatest impact at moderate task difficulty. The amphetamines have shown a "U" shaped effect that interacts with dopamine availability and catecholamine metabolism genotypes.[26,27] Our aim was to evaluate task-related fMRI as imaging biomarkers of drug effects. Specifically, we hypothesized that improved wakefulness following use of armodafinil in patients with OSA and residual sleepiness would be associated with increased activation in the executive function network using fMRI. We chose the volume of activation as the primary activation measure. Percent signal change in the activated voxels was the secondary imaging measure. Clinical and neuropsychological outcomes were also assessed as secondary measures. A key secondary outcome was mean response time for the 2-back working memory task that was used during fMRI.

The study evaluated, in a blinded, randomized, prospective, placebo-controlled design, the effect of brain activation during a working memory task, following the use of armodafinil in sleep apnea patients with severe persistent sleepiness despite absence of comorbidities and demonstrating effective use of CPAP therapy.

METHODS

Overview and Subject Selection

This was a 2-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with a 1- to 3-week screening period (**Figure 1**). This study received approval from the appropriate health authorities and the independent ethics committee/institutional review board at each site, and patients provided written informed consent after full explanation of the procedure. The study was conducted in full accordance with the Good Clinical Practice: Consolidated Guidance approved by the International Conference on Harmonisation[28] and any applicable national and local laws and regulations. Right-handed or ambidextrous men or women between the ages of 18 and 60 years with a current diagnosis of OSA (apnea-hypopnea index > 15/h of sleep) and a complaint of excessive sleepiness despite effective, stable CPAP usage defined as ≥ 4 h/night on ≥ 70% of nights (objectively verified using data from the CPAP device), were enrolled.

To be eligible, CPAP use must have been stable for ≥ 4 weeks prior to the beginning of the study. Other entry criteria included a mean sleep latency < 8 min on the multiple sleep latency test (MSLT),[29] an Epworth Sleepiness Scale (ESS) score ≥ 10 at the initial screening visit,[30] and an accuracy ≥ 80% on the 2-back working memory task during the screening period. Exclusion criteria included a history of or current use of central nervous system—active prescription medications, nicotine, chronic caffeine usage averaging more than ~ 400 mg/d (≥ 4 cups of coffee daily), National Adult Reading Test IQ < 90,[31] clinically significant depression or other psychiatric illness, uncontrolled medical condition, diagnosed sleep disorder other than OSA, positive urinary drug screen without medical justification, past or present seizure disorder, history of head trauma, and abnormal physical examination or laboratory parameters. The pre-treatment testing was administered within a week prior to starting armodafinil, and the post-treatment assessments were done on the final day of participation, which included the final scanning.

Drug Treatment

Armodafinil at a 200-mg dose was administered orally, once daily in the morning at or before 08:00, approximately 30 min before the first meal of the day. There was an up-titration period in which armodafinil 50 mg or matching placebo was given on day 1, increased to 100 mg/d on day 2, 150 mg/d on day 5, and 200 mg/d on day 8, which was the dosage that was then continued for the remainder of the double-blind treatment period for a total of 14 days.

Polysomnogram and MSLT

Polysomnographic and 5-session MSLT assessments were performed according to standard guidelines.[32,33] Stages,

arousals, and respiratory events were scored by polysomnography to confirm the efficacy of CPAP therapy, which was defined as an apnea-hypopnea index ≤ 10 per hour of sleep. Hypopneas were scored when associated with a 3% oxygen desaturation and/or an electroencephalographic arousal. The mean sleep latency was the latency to the first epoch of sleep. Polysomnographic data were used only to confirm inclusion criteria but were not otherwise collected or assessed during the study.

Neuropsychological Assessment

An abbreviated version of the Cambridge Neuropsychological Test Automated Battery (CANTAB) was used.[34] Executive function, processing speed, and episodic memory as measured by change from baseline in the performance of selected tasks (Motor Control Task, Reaction Time, Pattern Recognition Memory, and One Touch Stockings of Cambridge [OTS]) from the CANTAB were assessed at week 2 (or last post-baseline observation).

Functional Neuroimaging

Imaging was performed approximately 2 h after the study drug was taken, but no later than 11:00, to minimize circadian effects. Prior to each scanning session, patients were asked to rate their subjective sleepiness on a visual analog scale. Depending upon the recruitment site, imaging was performed with one of six 3 Tesla MRI scanners (4 General Electric and 2 Siemens) using the Functional Biomedical Research Network[35] protocol in which the scanning parameters were matched as closely as possible across sites.[36,37] Patients' baseline and final assessments were performed at the same site. Anatomical scanning was performed followed by functional scans (4 active-task runs). Whole-brain T1-weighted anatomical scans were acquired at each site for each subject. During anatomic scanning (and before functional runs when anatomic scanning was not performed), a modified continuous 10-min sustained attention task, similar to the psychomotor vigilance test (PVT)[38] but without performance feedback, was run to obtain a measure of vigilance in the scanner. For this task, the "+" symbol appeared on a screen at random (mean inter-trial interval of 5 s, range 2-10 s) but disappeared when a button was pressed. The attention tasks were run to obtain a measure of vigilance in the scanner as well as to keep patients awake while functional data were not being collected. For the task paradigm during the functional scanning runs, a block-design protocol was used, with 60 s "on-task" alternating with 30 s "off-task." Four whole-brain fMRI task runs were acquired for each patient at each visit. Scanning parameters included echo planar imaging, repetition time = 2000 ms, time to echo = 30 ms, flip angle = 77 degrees, bandwidth = 2298 Hz/pixel, 30 slices, slice thickness = 4 mm with a 1-mm gap, 64 × 64 matrix at 220 × 220 mm field of view, 285 time points, 9.5 min, sequential slice order.

Imaging Tasks

A 2-back working memory task was interleaved with a vigilance task. During the 60-s "on-task" periods, random letters were presented in the center of the visual field every 4 s, 15 for each 60-s block, and each stimulus lasted 500 ms. There were a total of 6 active-task blocks. During the 30-s "off-task" periods, the sustained attention task was performed that mirrored the 10-min sustained attention task. The task requires sustained vigilance and is not the same as a 0-back condition, for instance. The need to provide ongoing responses for this attention task also allowed the investigators to be certain that runs used did not contain sleep data—if a subject fell asleep, responses would stop and the scanning would also be stopped for that run.

Imaging Analysis

Anatomical image analysis was performed with FreeSurfer.[39-41] Specifically, a T1-weighted MP-RAGE (repetition time = 2300 ms, time to echo = 2.94 ms, inversion time = 1100 ms, flip angle = 9 deg, 0.86 × 0.86 × 1.2 mm^3) volume was collected for each subject and analyzed in FreeSurfer to create a mesh model of the cortical surface and generate subject-specific cortical[42,43] and subcortical[44] regions of interest (ROIs), including the anterior cingulate cortex (ACC), posterior parietal cortex (PPC), and thalamus. The dorsolateral prefrontal cortex (DLPFC) was defined as the middle frontal gyrus and sulcus and the inferior frontal sulcus using software-based automatic identification.[45] The surface-based ROIs were converted into volume-based ROIs by mapping them back into the anatomical volume and expanding them to fill the cortical ribbon.

The fMRI data were analyzed in the native fMRI volume using the FSL FEAT program in the FMRIB Software Library.[46,47] During preprocessing, each fMRI run was 3-dimensionally motion corrected to the middle time point and spatially smoothed by a 5-mm, full-width/half-maximum Gaussian filter for individual patient analysis. Statistical correlation maps were generated using a general linear model, in which the hemodynamic response to the 2-back task was modeled using the FEAT default gamma function and its derivative convolved with a 60-s boxcar. The vigilance periods were modeled as baseline. The FEAT analysis included temporal prewhitening to account for temporal autocorrelation. Significance maps testing 2-back > sustained attention task contrast were computed and thresholded at a voxel-wise uncorrected $p < 0.05$. The functional maps as well as the middle time point used for motion correction were registered to the subject's anatomical scan.[48] This allowed the thresholded maps to be converted into the anatomical volume space where the FreeSurfer volume-based ROIs were defined as described above. The number of voxels with $p < 0.05$ was counted in each ROI to provide the change in the primary efficacy measure (activation volume in mm^3 of the DLPFC) for each subject, visit, and run. A voxel count measure can often be less reliable due to variations in noise.[49-51] For this reason, we also computed the average percent signal change within the active voxels of the ROI as a secondary measure as this would be less sensitive to noise.[52]

Approach to Minimize Variability from Multi-institution and Multi-vendor fMRI

Collecting data from different scanning sites introduces the possibility of inconsistency both in the MRI acquisition and in the way the subject is handled. Several steps were taken to reduce these effects as suggested by the fBIRN

group[53]: (1) the field strength (all 3 Tesla) and parameters for the MRI protocols were matched as closely as possible; (2) each site collected data on a standardized phantom which was then used to measure scanner stability and noise[36]; (3) a single human was scanned at all sites using the complete study protocol just as if he were a real subject, and this person made suggestions as to how the subject experience could be made more consistent across sites; (4) the structural and fMRI data for this person were analyzed to show that similar results were obtained for the same subject across all sites; and (5) the MRI parameters for this data were also checked to assure they conformed to the study design before actual subject scanning began.

Study Measures

The primary efficacy measure was change in activation volume of the DLPFC from baseline to final visit, as measured by the activation volume measured by the number of voxels meeting the predefined threshold in the DLPFC on fMRI. The key secondary measure was mean performance speed, as measured by response latency, at the final visit for each group, on the 2-back working memory task performed during fMRI scanning.

Other secondary measures included (1) percent blood oxygenation level dependent (BOLD) signal intensity change in the DLPFC, ACC, PPC, and thalamus; (2) change from baseline to final visit in subjective efficacy measures, including the CANTAB, a modified continuous 10-min sustained attention task, ESS, Clinical Global Impression of Change (CGI-C),[54] and the Medical Outcomes Study 6-Item Cognitive Functioning Scale (MOS-CF6)[55]; and (3) correlations between the 2-back working memory task response latency and fMRI activation volume and percent signal change in the DLPFC, ACC, PPC, and thalamus.

Drug Tolerability

Tolerability was assessed by the occurrence of adverse events (AEs), concomitant medication usage, and change in vital signs.

Statistical Analysis

Sample Size and Power Considerations

The primary efficacy variable is the change from baseline in the number of voxels meeting predefined threshold in DLPFC on fMRI assessed at endpoint (week 2 or last post-baseline observation). The sample size calculation was based on the study results in Thomas and Kwong.[25] In their study, 8 healthy men were enrolled for a single-dose crossover study. Subjects were randomly assigned to 1 of 4 conditions (sleep deprived + a single dose of modafinil or placebo at 06:00, rested + modafinil or placebo). The sleep-deprived condition involved approximately 28 h of continuous wakefulness, and the rested condition included 8 h of scheduled sleep opportunity. Each subject was tested 4 times; all subjects were studied in each condition (32 separate experiments), counterbalanced with a washout period of a minimum of 1 week. The mean difference in the number of voxels was 14,231, and the standard deviation (SD) of the placebo treatment group was 11,107 (which was larger than that of the modafinil treatment group). The sample size calculation assumed an SD of 11,107 and a mean difference of 12,218. The assumption of the mean difference took into account the estimated enrollment rate (about 2 patients per center per month) and the timeline to complete the study while providing adequate power. With a standardized difference of 1.10 (12,218/11,107), 28 evaluable patients (≥ 14 per treatment group) are required to provide 80% power while controlling the 2-sided, type I error rate at 0.05. With an expected (estimated) 25% attrition rate, a total of 38 patients (19 per group) were planned to be enrolled in this study.

Analysis

The primary and key secondary variables were analyzed using analysis of covariance (ANCOVA), with treatment group, center, and sex as the fixed effects, and the baseline value as a potential covariate. The model assumptions for ANCOVA were tested, and if they could not be established, Wilcoxon rank sum test was used. Regarding demographic and baseline characteristics, treatment groups were compared for continuous variables using an analysis of variance with treatment groups as fixed factors. Categorical variables were summarized using descriptive statistics. Treatment groups were compared for all categorical variables using Fisher's exact test (because of small sample sizes).

RESULTS

Baseline Characteristics

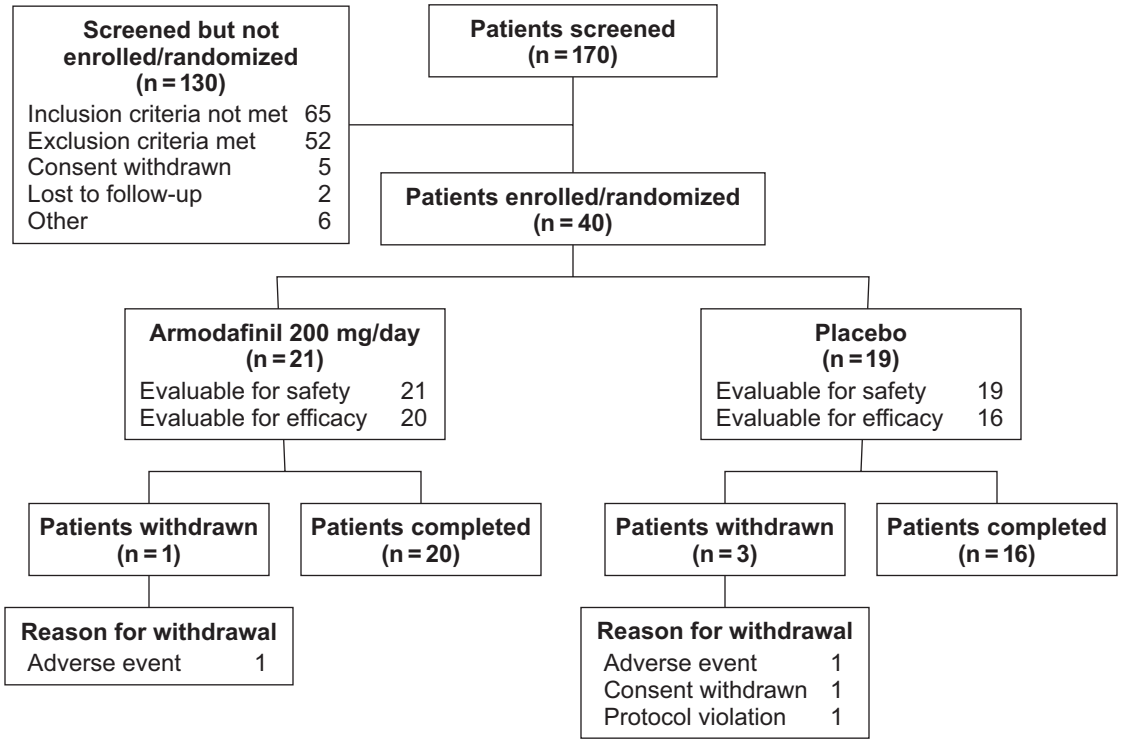
A total of 170 patients with OSA were screened for the study; 40 were enrolled and assigned to randomized, double-blind treatment with either armodafinil (n = 21) or placebo (n = 19) (**Figure 2**). All 40 enrolled patients received at least one dose of study drug and were evaluated for safety; 36 (90%) patients completed the study, were included in the final analysis, and evaluated for efficacy, including 20 patients in the armodafinil group and 16 in the placebo group (**Figure 2**).

Demographic characteristics were similar between the armodafinil and placebo groups (**Table 1**). Baseline clinical characteristics were also generally similar, due in part to the study inclusion criteria (**Table 1**). On the Clinical Global Impression of Severity (CGI-S) scale, the majority of patients were rated as either moderately ill (57% and 42%) or markedly ill (33% and 42%) in the armodafinil and placebo groups, respectively. Mean (standard deviation [SD]) CPAP usage during screening was 6.7 (1.17) h per night for the armodafinil group (n = 19) and 6.1 (1.48) h per night for the placebo group (n = 18). No alcohol use was reported by 48% of patients in the armodafinil group and 68% of those in the placebo group. While no patients in the armodafinil group reported caffeine use during the 48 h prior to baseline, 3 (16%) patients in the placebo group reported consuming between 1 and 199 mg of caffeine during that period (**Table 1**).

Compliance with Treatment

Compliance was assessed again during the run-in period leading to study participation. All subjects were highly compliant, averaging 6.4 h of CPAP use per night during a

Figure 2—Patient disposition.



1-week period. During the study, no patients discontinued due to noncompliance to either the study medication or procedures.

Polysomnography and MSLT

At baseline, all patients had an apnea-hypopnea index of ≤ 10/h of sleep. Mean (SD) MSLT was 5.4 (1.56) min in the armodafinil group and 6.1 (1.32) min in the placebo group.

Imaging Results

Figure 3 shows the general areas activated by the task. These activation maps were a random-effect group analysis[56] (all subjects, all visits) of the 2-back vs. sustained attention task contrast projected onto the inflated cortical surface. The maps were thresholded at $p < 0.05$, cluster-wise corrected for multiple comparisons (cluster forming threshold at $p < 0.01$).[57] Yellow indicates that the 2-back hemodynamic response amplitude was greater than that of sustained attention task; blue indicates the opposite. The green line indicates the boundary for DLPFC used in the study. In both hemispheres, there was strong task-positive activation in the DLPFC. In addition, there was bilateral task positive activation in the following areas: calcarine sulcus, superior parietal, anterior insula, and the medial wall of the superior frontal area. There was also task-positive activation in the left hemisphere in the motor area (subjects responded with their right hand). There were wide areas of task-negative activation in expected default mode areas: inferior parietal, posterior cingulate, precuneus, and medial frontal, as well as lateral occipital and insula. These results indicated that the brain is well activated in areas expected for this task. **Figure 4** shows the same activation maps broken down by group and visit (uncorrected p values thresholded at $p < 0.01$).

Efficacy

Primary Imaging Efficacy Measure

The primary efficacy measure, activation volume of the DLPFC, was reduced from baseline to final visit in both treatment groups; however, the changes were not significantly different between groups ($p = 0.74$, Wilcoxon rank sum test; **Figure 5**). To further explore this finding, a post hoc analysis of image quality was performed by computing signal-to-fluctuation-noise ratio (SFNR) as the mean intensity divided by the time series residual SD.[58] An average SFNR value was calculated for the DLPFC. This analysis indicated a reduction in the SFNR from baseline to final visit in both groups (placebo baseline SFNR = 203, final SFNR = 185; armodafinil baseline SFNR = 179, final SFNR = 168) perhaps due to an increase in motion artifact at the final visit.

Secondary Imaging Efficacy Measures

Analysis of the key secondary variable, change from baseline in mean response latency for the 2-back working memory task at the final visit, showed that the mean (SD) changes in latency of 2.3 (78.94) ms for the armodafinil group and -59.0 (112.69) ms for the placebo group were not statistically different ($p = 0.17$, Wilcoxon rank sum test). A decline in activation volume was observed for the ACC, PPC, and thalamus in each group. The decrease was significant within each group ($p < 0.01$), but was not significantly different between groups ($p < 0.30$).

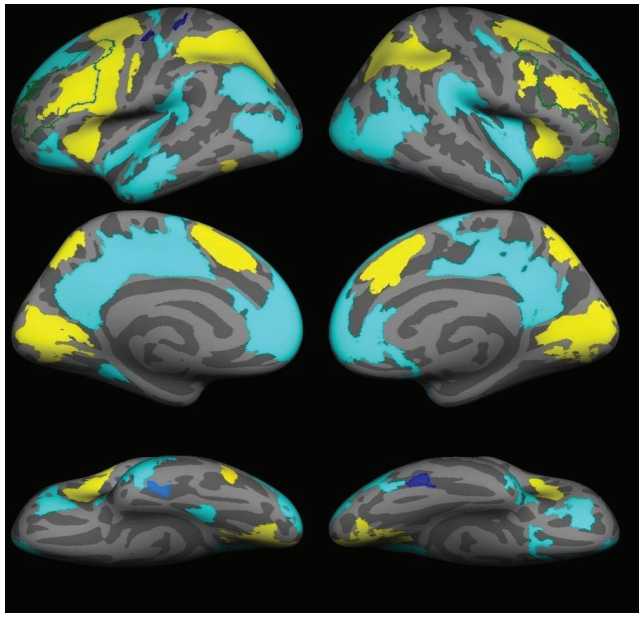
With regard to other secondary variables, no change from baseline was observed in the difference in the BOLD signal between the working memory and the sustained attention task blocks in the DLPFC, ACC, PPC, or thalamus. Exploratory spatial (e.g., voxel-wise) analyses were also conducted. These

Table 1—Baseline demographic and clinical characteristics

Demographic characteristic	Armodafinil 200 mg/d (n = 21)	Placebo (n = 19)	p
Age, y, mean (SD)	49.9 (8.98)	50.7 (7.95)	0.7739[a]
Sex, n (%)			
Male	17 (81)	14 (74)	0.7116[b]
Female	4 (19)	5 (26)	
Race, n (%)			
White	17 (81)	16 (84)	0.6978[b]
Black	1 (5)	2 (11)	
Asian	3 (14)	1 (5)	
BMI, kg/m^2, mean (SD)	33.4 (6.78)	32.1 (6.17)	0.5306[a]
Clinical characteristic	**Armodafinil 200 mg/d (n = 21)**	**Placebo (n = 19)**	**Total**
CPAP usage, h/night, mean (SD)[c]	6.7 (1.17)	6.1 (1.48)	6.4 (1.35)
MSLT, min, mean (SD)	5.4 (1.56)	6.1 (1.32)	5.7 (1.48)
CGI-S, n (%)			
Normal (shows no signs of illness)	0	0	0
Borderline ill	0	0	0
Mildly (slightly) ill	1 (5)	1 (5)	2 (5)
Moderately ill	12 (57)	8 (42)	20 (50)
Markedly ill	7 (33)	8 (42)	15 (38)
Severely ill	0	2 (11)	2 (5)
Among the most severely ill	1 (5)	0	1 (3)
Alcohol usage, n (%)			
None	10 (48)	13 (68)	23 (58)
1-6 units per week	11 (52)	5 (26)	16 (40)
7-14 units per week	0	1 (5)	1 (3)
More than 14 units per week	0	0	0
Caffeine usage per day over prior 48 h, n (%)			
None	21 (100)	16 (84)	37 (93)
1-199 mg	0	3 (16)	3 (8)
ESS score, mean (SD)[d]	14.6 (3.28)	16.8 (2.86)	15.5 (3.13)

BMI, body mass index; CGI-S, Clinical Global Impression of Severity; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; MSLT, multiple sleep latency test; n, sample size; SD, standard deviation. [a]Comparison is from an analysis of variance with treatment group as a factor. [b]Comparison is from the Fisher exact test. [c]Armodafinil, n = 19; placebo, n = 18. [d]Baseline values in patients evaluable for efficacy, including 20 patients who received armodafinil and 16 patients who received placebo.

Figure 3—Significance maps of the 2-back vs. sustained attention task contrast (all subjects, all visits) projected onto the inflated cortical surface and thresholded at p < 0.05, cluster-wise corrected for multiple comparisons.



Yellow indicates that the amplitude of the 2-back hemodynamic response was greater than that of sustained attention task; blue/cyan indicates the opposite polarity. The green line is the definition of dorsolateral prefrontal cortex for this study.

showed no statistically significant differences, including direct contrast between groups, between visits, or for the interaction of group and visit.

Neuropsychological Testing

In CANTAB measures of cognitive function, there were no substantial changes from baseline to final visit for most tasks in either treatment group (**Table 2**). For mean "latency to correct" on the OTS task ("difficult" tasks, defined as tasks requiring a 4- to 6-move average), the placebo group had a larger median improvement than the armodafinil group (-8058.0 ms vs. -227.3 ms, respectively; p = 0.02, Wilcoxon rank sum test).

Sustained Attention and 2-Back Working Memory Task

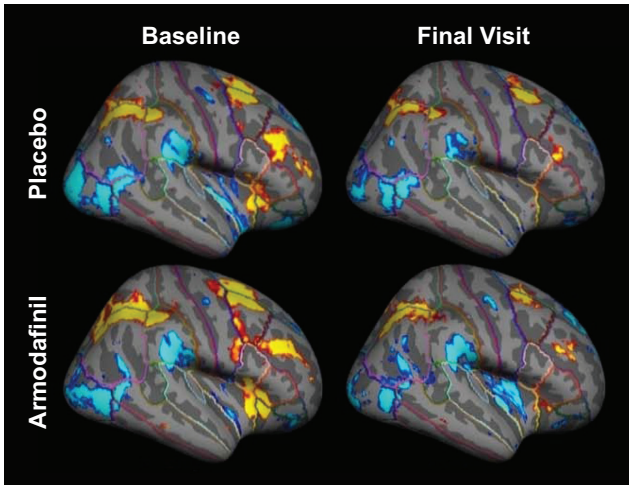
Results for the modified continuous 10-min sustained attention task showed that patients in the armodafinil group had numerically faster (although not statistically different) responses. From mean (SD) baseline mean latency values of 343.1 (50.2) ms and 373.3 (73.8) ms for the armodafinil and placebo groups, respectively, mean times decreased to 332.1 (55.3) ms for the armodafinil group while increasing to 377.1 (74.9) ms in the placebo group. At final visit, the mean decrease in time was -17.7 (39.6) ms for the armodafinil group, compared with a mean increase of 4.6 (41.4) ms in the placebo group (p = 0.13, ANCOVA). However, mean response latencies for the 2-back working memory task increased in the armodafinil group from 790.1 (223.6) ms at baseline to 792.4 (214.9) ms at final visit compared with a decrease from 966.5 (322.0) ms at baseline to 907.5 (306.7) ms at final visit for the placebo group. Mean differences were 2.3 (78.9) ms in the armodafinil group and -59.0 (112.7) ms in the placebo group.

Subjective Measures

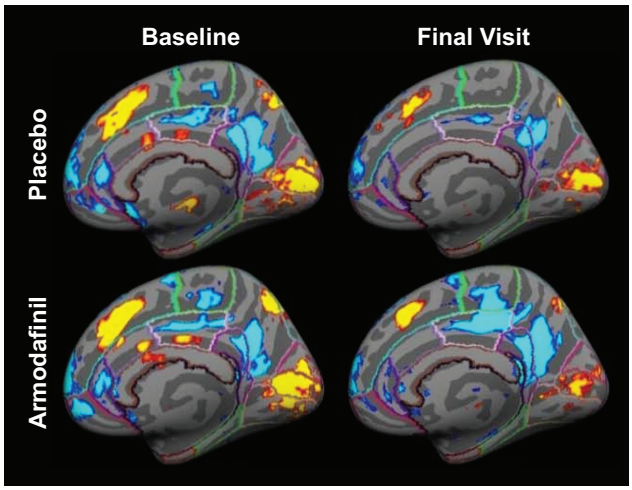
Among subjective efficacy measures, the CGI-C ratings for excessive sleepiness showed that 65% of patients in the armodafinil group were classified as responders (rated as "minimally," "much," or "very much" improved), compared with 56% of the placebo group (p = 0.73, Fisher exact test). The armodafinil group showed greater reduction in excessive sleepiness with a mean (SD) change in ESS score from baseline to final visit of -5.2 (4.53), compared with -3.4 (4.53) for placebo (p = 0.0499, ANCOVA). In addition, patient-reported cognitive functioning as measured by the MOS-CF6 also reflected a mean improvement in the armodafinil group from baseline to final visit of 9.2 (14.82)

Figure 4—Significance maps of the 2-back vs. sustained attention task contrast at baseline and final visit for each group.

A. Group Hemodynamic Response: Right Hemisphere Lateral View



B. Group Hemodynamic Response: Right Mid-Sagittal View



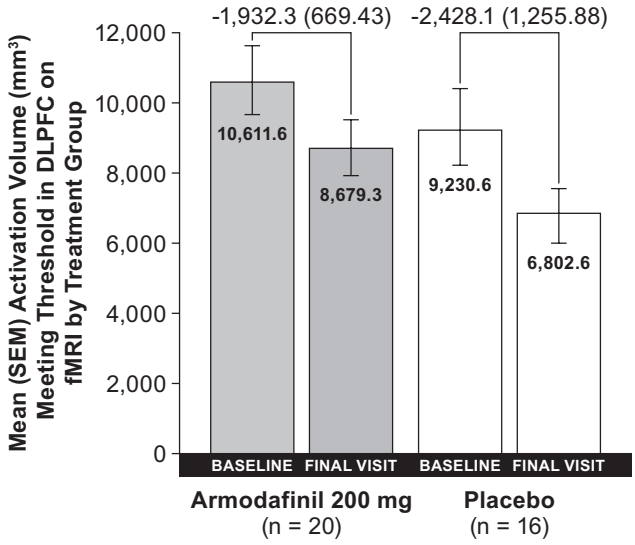
(A) Group hemodynamic response: right hemisphere lateral view. **(B)** Group hemodynamic response: right mid-sagittal view. The maps are thresholded at $p < 0.01$ (uncorrected for multiple comparisons). Red/yellow indicates that the amplitude of the 2-back hemodynamic response was greater than that of sustained attention task; blue/cyan indicates the opposite polarity.

points compared with a decline of -0.8 (6.86) points for the placebo group, although this difference was not significant ($p = 0.12$, ANCOVA).

Activation-Performance Correlations

Analysis of correlations between fMRI results in the DLPFC, ACC, PPC, and thalamus and response latency for 2-back working memory task generally showed high variability and few statistically significant correlations (**Table 3**). In the armodafinil group, however, activation volumes were positively correlated with response latency for all of these regions, both at baseline and final visit. In the placebo group, in contrast,

Figure 5—Mean (SEM [standard error of the mean]) change from baseline in functional activation volume (1 mm^3) meeting threshold in DLPFC (dorsolateral prefrontal cortex) on fMRI (functional magnetic resonance imaging).



Change from baseline with armodafinil vs. placebo, $p = 0.74$, Wilcoxon rank sum test.

activation volumes were positively correlated at baseline and negatively correlated at final visit.

Tolerability

Armodafinil was found to be generally well tolerated during this trial. During the double-blind treatment period, 13 (62%) patients in the armodafinil group and three (16%) patients in the placebo group reported at least one AE (**Table 4**). The corresponding number of treatment-related AEs (as judged by the investigator) was nine (43%) for patients in the armodafinil group and three (16%) in the placebo group. Most AEs were mild in severity, and no severe AEs, deaths, or other serious AEs were reported during the study. Two (5%) patients were withdrawn from the study because of AEs, one (5%) in the armodafinil group due to headache and nausea (both of which were considered by the investigator to be of moderate severity and probably related to the study drug) and one (5%) in the placebo group due to urticaria and anxiety (both of which were mild in severity and considered by the investigator to be probably related to the study drug). The most frequently occurring AE in the armodafinil group was headache (**Table 4**). The only other AEs reported in more than one patient in the armodafinil group were nasopharyngitis and diarrhea. No AEs were reported for more than one patient in the placebo group.

DISCUSSION

The key result of our study was that armodafinil treatment for 14 days did not change functional brain activation or improve cognitive performance, in a variety of primary and secondary measures, in treated patients with OSA and persistent excessive sleepiness. The subjects for this study were

Table 2—CANTAB results

Task	Group[a]	Baseline	Endpoint	Median change	p
PRM delayed (median % correct)	Armodafinil	92.0	92.0	0.0	0.712
	Placebo	92.0	96.0	0.0	
PRM immediate (median % correct)	Armodafinil	100.0	100.0	0.0	0.246
	Placebo	100.0	100.0	0.0	
RTI 5-choice (median, ms)	Armodafinil	321.5	318.5	-6.5	0.610
	Placebo	330.0	317.0	-12.5	
RTI 1-choice (median, ms)	Armodafinil	284.5	278.0	-13.5	0.962
	Placebo	292.5	305.0	-4.5	
OTS easy (median, ms)	Armodafinil	6,017.0	4,879.2	-673.3	0.454
	Placebo	5,758.2	5,498.7	-394.2	
OTS hard (median, ms)	Armodafinil	25,483.7	28,110.5	-227.3	0.019
	Placebo	32,793.7	24,762.2	-8,058.0	
OTS easy (median choices to correct)	Armodafinil	1.1	1.0	0.0	0.170
	Placebo	1.0	1.0	0.0	
OTS hard (median choices to correct)	Armodafinil	1.4	1.2	-0.1	0.061
	Placebo	1.3	1.3	0.1	

CANTAB, Cambridge Neuropsychological Test Automated Battery; OTS, One Touch Stockings task; PRM, pattern recognition memory; RTI, reaction time.
[a]Comparison is from an analysis of variance with treatment group as a factor.

Table 3—Correlation coefficients [a] for fMRI variables and performance on the 2-back working memory task

	Activation Volume		BOLD Signal Intensity	
	Armodafinil[b]	Placebo[b]	Armodafinil[b]	Placebo[b]
DLPFC				
Baseline (p[c])	0.493 (0.023)	0.400 (0.115)	-0.228 (0.327)	0.357 (0.164)
Final Visit (p[c])	0.422 (0.057)	-0.445 (0.075)	-0.122 (0.603)	0.789 (< 0.0001)
ACC				
Baseline (p[c])	0.445 (0.043)	0.185 (0.485)	0.009 (0.971)	0.571 (0.016)
Final Visit (p[c])	0.254 (0.273)	-0.152 (0.567)	0.025 (0.917)	-0.012 (0.964)
PPC				
Baseline (p[c])	0.328 (0.149)	0.371 (0.147)	0.036 (0.877)	0.408 (0.107)
Final Visit (p[c])	0.355 (0.117)	-0.358 (0.163)	0.065 (0.781)	0.364 (0.156)
Thalamus				
Baseline (p[c])	0.308 (0.178)	0.453 (0.069)	-0.106 (0.651)	0.651 (0.004)
Final Visit (p[c])	0.405 (0.069)	-0.038 (0.888)	-0.029 (0.901)	0.582 (0.014)

All estimations are based on Fisher z-transformation. ACC, anterior cingulate cortex; BOLD, blood oxygenation level dependent; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; PPC, posterior parietal cortex. [a]Correlation coefficient is Pearson correlation coefficient. [b]Patients with fMRI results included; 20 patients treated with armodafinil, 16 patients treated with placebo. [c]p values calculated from PROC CORR procedure for testing correlation coefficient = 0.

highly selected, excellent users of CPAP, and free of comorbid illnesses such as depression and circadian rhythm disorders. There was an unexplained reduction in signal/noise during the second scanning session in both treatment and placebo groups, and a reduction in activation volumes in both groups during the second scanning session. These two phenomena are probably related because a reduction in the SFNR will cause a drop in activation volume that exceeds a given p-value threshold. As these were patients well treated with CPAP without associated cardiopulmonary morbidity, it is unlikely that undetected hypercapnia altered the imaging findings.

Armodafinil has consistently been shown to provide clinical benefits in those with narcolepsy, sleep apnea, shift work sleep disorder, and jet lag.[15-17,59-61] Lack of a response to both objective and subjective measures has several possible explanations. The study may have been underpowered given the inter-individual variability in sensitivity to sleepiness seen in OSA patients (for given degrees of sleep apnea severity) and experimental sleep deprivation.[62,63] Armodafinil did not show adequate clinical effectiveness in this subset of patients (CGI-C scores were not significantly changed), and the imaging findings may have reflected that fact.

The design of the baseline imaging task may also have contributed to the negative result. The contrast was a 2-back vs. an active attention baseline that closely mimicked the classic PVT.[38] It is possible that the cognitive effort required

to adequately perform the PVT-like task was so high in these patients with severe persistent sleepiness that they did not have the cognitive resources/reserve to perform the 2-back. That is, both the baseline and 2-back condition may have been about equally difficult. Different results may have been obtained if the baseline was a 0-back or fixation condition.

The unexplained signal/noise factor is an additional possibility. The duration of treatment may have been too short, as it takes several days for armodafinil to reach steady state.[64] Although prior imaging work in healthy individuals with modafinil does suggest rapid effects,[65,66] patients with OSA may be different. A sluggish BOLD response in sleep apnea from abnormal cerebrovascular reactivity may also be considered, but the imaging findings were consistent with the minimal noted subjective benefits.

The findings of non-response to treatment may support the hypothesis that the brain in those with persistent sleepiness despite good sleep apnea treatment shows features of permanent injury and impaired neurocircuitry.[8,67,68] Gray or white matter dysfunction and recovery has implications in adults and children for cognitive outcomes such as age-related cognitive change, cognitive development, affective disorders, and learning/memory, besides just subjective sleepiness. Additionally, the reversibility of sleep apnea's effects on the body is an important issue, given the spectrum of cardiovascular, metabolic, and neurological abnormalities demonstrable in untreated patients.

Patients in this study were long-term users of CPAP treatment yet were very sleepy subjectively and objectively. The degree of objective sleepiness exhibited was in the range seen in narcolepsy.[33] This may very well be an extreme group in a pathological sense, especially given high compliance and polysomnographic treatment efficacy. However, the threshold apnea-hypopnea index of 10, though including the arousal criterion, may have some residual disease and the standard deviations of CPAP use (6.4 ± 1.35), which indicates that about 15% of patients used CPAP for 5 hours or less. Real-life contributions to residual sleepiness include some unprotected (from sleep apnea) sleep time, depression, and behavioral sleep restriction. While both the armodafinil and placebo treatment groups showed a reduction from baseline to final visit in the primary efficacy measure, DLPFC activation volume, no substantial changes were observed in either group in cognitive function. Working memory task performance times in this study were relatively slow, a finding similar to those of an earlier fMRI study[20] in which patients with OSA had significantly longer reaction times than healthy controls (908 ms vs. 596 ms; $p < 0.02$). In that study, although rigorous treatment with CPAP therapy completely resolved subjective sleepiness, there was no significant effect on working memory task performance, suggesting that there may be dissociations between respiratory and cortical recovery in OSA.[20]

There are numerous experimental data in animal models showing mechanisms of neuronal injury from intermittent hypoxia.[11,12,69-71] Sleep apnea in humans is associated with several abnormalities that have the potential to cause gray and white matter injury.[10,73-75] These include nocturnal hypertension/non-dipping blood pressure patterns prior to diagnosis, hypoxia-related injury, metabolic syndrome, and cytokine dysregulation.[4,5,10] Sleep deprivation and sleep fragmentation impair hippocampal neurogenesis and long-term potentiation.[76,77]

Table 4—Adverse events occurring in at least 5% of the armodafinil group and at a higher rate than in the placebo group

Adverse event, n (%)	Armodafinil 200 mg/d (n = 21)	Placebo (n = 19)
Headache	4 (19)	1 (5)
Nasopharyngitis	3 (14)	0
Diarrhea	2 (10)	0
Abdominal pain (upper)	1 (5)	0
Angina pectoris	1 (5)	0
Bruxism	1 (5)	0
Cardiac murmur	1 (5)	0
Chest discomfort	1 (5)	0
Cough	1 (5)	0
Energy increased	1 (5)	0
Heart rate increased	1 (5)	0
Hypoesthesia	1 (5)	0
Irritability	1 (5)	0
Nausea	1 (5)	0
Polyuria	1 (5)	0
Seasonal allergy	1 (5)	0
Tachycardia	1 (5)	0
Upper respiratory tract infection	1 (5)	0

Reversibility of brain function or structural impairment/change is an important clinical issue in sleep apnea. Structural and fMRI and magnetic resonance spectroscopy have been used to assess reversibility. At least partial reversibility has been demonstrated in those who have clinical response to treatment,[78] but there is a real concern that full reversibility may not occur. If our study subjects are at one end of the spectrum, the neurological effects of sleep apnea on the brain can be thought of as a continuum, starting at purely functional with reversible deficits, progressing to clinical reversibility but demonstrable persistent neuroanatomical or functional alterations, to a final state of loss of compensatory activity with poor response to stimulants associated with permanent neurological injury. Sleep apnea thus may have the potential to cause lasting brain injury and this population of highly treatment compliant patients with severe objective persistent sleepiness without other comorbid factors may reflect this outcome.

CONCLUSION

Armodafinil did not improve fMRI measures of prefrontal cortical activation during a working memory task or mean performance speed in the 2-back working memory task, compared with placebo, in patients with OSA who were experiencing persistent excessive sleepiness despite effective, stable CPAP treatment. Armodafinil was generally well tolerated.

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