Does Armodafinil Improve Driving Task Performance and Weight Loss in Sleep Apnea? A Randomized Trial

RUNNING TITLE: DIET, EXERCISE AND ARMODAFINIL FOR OSA (DEAR)

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with obstructive sleep apnea (OSA) who are unable to use standard treatments are left with few alternatives. Weight loss may reduce OSA severity but this takes time during which daytime sleepiness remains. Armodafinil is a wakefulness promoting agent that is used to treat daytime sleepiness in a range of conditions, but has never been used previously in this population.

What this Study Adds to the Field

In overweight, sleepy patients with OSA unable to use standard treatments, simulated driving ability improved with armodafinil at three but not six months. The use of armodafinil resulted in greater reduction in body fat than placebo.

Armodafinil should be considered as an adjunct during weight loss in patients who do not use mechanical treatment for OSA and may improve daytime performance for between three and six months.

ABSTRACT

RATIONALE

Obstructive sleep apnea (OSA) patients unable to tolerate standard treatments have few alternatives. They may benefit from weight loss, but the major symptom of daytime performance impairment may remain during weight loss programs.

OBJECTIVES

We hypothesized that wakefulness-promoter armodafinil would improve driving task performance over placebo in patients undergoing weight loss.

METHODS

Placebo-controlled, double-blind, randomized trial of Armodafinil vs Placebo daily for 6 months in patients who were also randomized to one of two diets for six months with follow-up at one year in overweight, adult, OSA patients who had rejected standard treatment and suffered daytime sleepiness.

MEASUREMENTS

Primary outcome: change in steering deviation in the final 30 minutes of a 90 minute afternoon driving task (AusED) at six months. Secondary outcomes: Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, fat mass measured by dual-emission X-ray absorptiometry (DXA).

MAIN RESULTS

Armodafinil improved driving task performance over placebo at three months (12.9cm, 95%CI 4.1 to 21.7, p=0.004), but not the primary timepoint of six months (5.5cm, 95%CI -3.3 to 14.3, p=0.223). Patients on armodafinil lost 2.4kg more fat than those on placebo at six months (95%CI 0.9 to 4.0, p=0.002). Other secondary outcomes were not significantly improved.

CONCLUSIONS

Armodafinil did not improve driving task performance at the primary endpoint of six months. Armodafinil might be a useful adjunctive to weight loss in OSA patients rejecting conventional treatments but this needs to be directly tested in a specifically designed, properly powered clinical trial.

Trial Registration

This trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry ACTRN12611000847910.

Some of the results of this study have been previously reported in the form of abstracts.(1-4)

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INTRODUCTION

Obstructive sleep apnea (OSA) is associated with excessive daytime sleepiness,(5) neurocognitive dysfunction and motor vehicle accidents.(6, 7) The traditional first-line therapies for OSA, continuous positive airway pressure (CPAP) and mandibular advancement splints (MAS), are initially expensive and require individual titration. Many OSA sufferers who are recommended CPAP or MAS either do not initiate or maintain treatment leaving a large number of patients untreated and often lost to follow-up.(8) Obesity is one of the key causes of OSA, and when weight loss is achieved it may be effective as an alternative for these patients.(9, 10) Two common diets popular with clinicians in our region are the Australian Guide to Healthy Eating (AGHE), based upon national guidelines(11) and similar to the American Dietary Guidelines "Choose My Plate"(12) and the low-GI high-protein (LGHP) diets.(13)

While weight loss can be efficacious, it can take time, during which symptoms of daytime sleepiness and dysfunction may persist in patients with OSA. Wakefulness promoters modafinil and armodafinil (the R-enantiomer which results in higher plasma concentrations late in the day)(14) have been trialled extensively adjunctive to CPAP when patients still suffer residual excessive daytime sleepiness.(15) This is one of the listed indications in both Australia and the USA.(15-17) But despite sporadic reports of weight loss or anorexia(18) associated with modafinil/armodafinil neither medication has been deliberately tested in conjunction with a weight loss program. Neither have they been tested in a randomized trial of longer than 3 months.(15)

We aimed to treat patients with either 6 months of armodafinil or placebo to manage sleepiness and neuropsychological dysfunction while undergoing a weight loss program followed up at 12 months. Our primary hypothesis was that armodafinil would improve driving task performance at six months over placebo. Our secondary hypotheses were that armodafinil would improve subjective daytime sleepiness, sleepiness related quality of life, and cause greater fat mass loss over placebo.

METHODS

This randomized, placebo-controlled, parallel-group trial was conducted between June 2012 and October 2015 at the Woolcock Institute of Medical Research and Royal Prince Alfred Hospital (RPAH), Sydney Australia. Sydney Local Health District (RPAH) Human Research Ethics Committee approved the protocol (X11-0088).

The trial protocol was prospectively registered with the Australian/New Zealand Clinical Trials Registry (ACTRN12611000847910).

Males and females aged 18-70 were recruited from the Woolcock Sleep Disorders Clinic and Database, the community via radio, print advertising, and media coverage. Inclusion criteria: at least moderate (apnea hypopnea index (AHI)≥15), symptomatic OSA (Epworth Sleepiness Scale (ESS)≥10 or clinician report of excessive daytime sleepiness), rejected treatment with CPAP/MAS, overweight-moderately obese [(body mass index (BMI)≥27kg/m^2 or waist ≥80cm (women) or ≥94cm (men)) but BMI<40kg/m^2 and weight<130kg (DXA scanner weight limitation)], current drivers' licence. Exclusion criteria: overnight shift-workers, unstable cardiac or psychiatric conditions, central sleep apnea, blood pressure (BP)>180/110mmHg, or severe eczema. See the Supplementary Methods for a complete list of the inclusion and exclusion criteria.

The randomization schedule was generated electronically by a statistician who played no further role in the study in a 1:1 ratio for both armodafinil:placebo and the AGHE:LGHP diet. Patients, study staff and the data analysts were blinded to drug but not diet allocation. DXA scans were scored by an investigator blinded to drug and diet allocation.

Patients were given 3x50mg tablets (armodafinil/matched placebo) each morning before breakfast for 6 months. Between 6 and 9 months all patients were given placebo. Under the care of a dietitian, patients were randomly allocated to either the AGHE or LGHP diet, which were expected to result in equivalent weight loss.(11, 19) All patients were given exercise advice to reduce weight.(20) Diet and drug treatments were started concurrently immediately after the baseline measurements.

Potential participants were telescreened via telephone or email before attending a physician-led consent and screening visit. Eligible patients were enrolled for eight visits and one phone call over 12 months (Supplementary Figure: S-1). The primary outcome was the change in steering deviation from the median lane position on the AusED driving task(21) in the final 30 minutes of a 90-minute afternoon drive at the six month visit. The secondary outcomes were: daytime sleepiness and sleepiness-related quality of life measured by the ESS(22) and Functional Outcomes of Sleep Questionnaires (FOSQ),(23) and total fat mass measured by DXA.

Adverse event reports were collected spontaneously and at each visit. Further information can be found in the supplementary methods. Routine blood tests (biochemistry, haematology, glucose and insulin),resting BP, and heart rate (HR) were measured at each visit.

Additional methods can be found in the online supplement.

Statistical Analyses

Statistical analyses were performed on all enrolled patients according to the intention-to-treat principle(24) in SAS 9.4 (SAS Institute, Cary, NC) using mixed model analysis of variance. The a-priori power calculation showed that 130 patients, with an allowance for a dropout of 18 patients, were required to detect a 6cm difference in improvement in steering deviation on a background of 11.3cm SD with Alpha=0.05, Power=0.8. The expected effect size (0.53) is similar to that seen in a previous trial of modafinil in OSA patients acutely withdrawn from other treatment,(25) and similar to the combined effect of sleep restriction and OSA on the same driving task parameter.(26) Normal steering deviation during a 90 minute AusED in non-OSA controls is 36.5 ± 9.2cm and therefore 6cm represents approximately 16% of that value which we believe is clinically meaningful.(27) Additionally, an effect size of approximately 0.5 is generally considered to reflect a clinically important change.(28)

Pre-planned per-protocol analyses were performed for the primary and secondary outcomes. This was defined as whether or not a patient took the study medication on the day of testing (simulated driving task). For the secondary outcomes (ESS, FOSQ, fat mass), medication adherence was calculated based upon the number of tablets returned at each three monthly visit and participants were split into quartiles from least to most adherent. Further information can be found in the online supplement.

RESULTS

Patient recruitment is described in Figure 1. See Supplementary Figures S-2-S-3 and Tables S-1-S-2 for reasons patients were excluded. Recruitment ceased in October 2014 as funding for the trial was exhausted when 113 of the intended 130 patients were enrolled. Patients were overweight, predominantly male, middle-aged and mildly hypertensive (Table 1). Complete data was available for the primary outcome (AusED) at 6-months for 87 patients (Figure 1).

Steering deviation in the final 30 minutes of the 90 minute drive was not better on armodafinil at six months (5.5cm improvement over placebo, 95%CI -3.3 to 14.3, n=87 p=0.223, see Figure 2). However at 3 months there was significant improvement on armodafinil over placebo (12.9cm, 95%CI 4.1 to 21.7, p=0.004). Per-protocol analysis (i.e. those participants who took drug on the day of testing) showed that 6-month driving task performance was still not statistically improved over placebo (6.5cm, 95%CI -1.9 to 15.1, p=0.130, Supplementary Figure S-6). There was no interaction between diet and drug for the primary outcome (p=0.85). There was no difference between the groups in the single blind run-out phase at 9-months (See Supplementary Table S-3 and Figure S-7).

Patients lost 4.6kg fat mass overall at 6 months (95%CI 3.7 to 5.5) and sustained fat loss to 12 months of 4.1kg (95%CI 3.1 to 5.1, n=81). The difference between the AGHE and LGHP diets was within the predefined equivalence margins (0.58kg, 95%CI -1.04 to 2.19, see Supplementary Figure S-8). There was no interaction between diet and drug for fat mass (p=0.96). Fat mass loss correlated with improvement in AHI at 12 months (r=0.416, p=0.0002, Supplementary Figure S-19). Those on armodafinil lost 2.4kg more fat than those on placebo (95%CI 0.9 to 4.0, p=0.002, See Figure 3). 47% of armodafinil patients lost ≥5% weight and 24% lost ≥10% weight at 6 months compared with 21% and 9% of patients on placebo respectively. There was some fat and weight regain during the placebo run-out and follow-up periods (See Figures S-8 and S-9) so that there was no difference between armodafinil and placebo groups at 12 months. Neither Epworth nor FOSQ were significantly improved by armodafinil (see Table 2 and Supplementary Figures S-10 and S-11). No tertiary outcome was significantly improved by armodafinil except that armodafinil increased activity counts measured by wrist actigraphy (See Table 2). Patients on armodafinil lost 2.9kg more fat than those on placebo at six months (95%CI 0.9 to 4.8, p=0.004) but AHI was not different between the groups (see Table 2).

Patients in the highest quartile of adherence with armodafinil did not improve on ESS (1.9 points, 95%CI -0.2 to 4.0, p=0.074) but had an 11.8 point improvement in FOSQ (95%CI 2.9 to 20.1, p=0.011) compared to those in the highest quartile of adherence with placebo (See Supplementary Figures S-12 and S-13).

The placebo group increased activity 8.8% from baseline, the armodafinil group increased activity 17.5% from baseline (difference 28,800 counts/day, 95%CI 576 to 57,024, p=0.045, see Supplementary Figure S-14). The three factor eating questionnaire was not different between groups at any timepoint (see Supplementary Table S-4).

SAFETY

There were no deaths. There were 14 serious adverse events (SAEs) reported in the 6-month drug trial by 12 participants; nine on armodafinil and five on placebo (Relative risk (RR)=1.78, 95%CI 0.63 to 5.0, p=0.28). None were deemed related to study medication by the investigators. Nine participants ceased study medication or withdrew due to an adverse event (AE), eight on armodafinil and one on placebo (RR=7.49, 95%CI 0.97 to 58.10, p=0.054, see Supplementary Results for further details). 95 participants suffered at least one AE not meeting the above criteria, 50 (91%) patients on armodafinil and 45 (78%) patients on placebo (RR=1.09, 95%CI 0.81 to 1.47, p=0.57). Overall there were 188 AEs reported on armodafinil and 125 reported on placebo (RR not calculable as data not independent, some patients reported up to 16 AEs across the six months). AEs that occurred in more than 5% of patients are listed in Table 3 and a complete list of AEs is in Supplementary Table S-6.

Systolic (SBP) and diastolic (DBP) blood pressure was reduced in conjunction with the diets on both armodafinil and placebo but the size of the reduction was smaller on armodafinil at 3 months but not 6 months (See Table 2 and Supplementary Figures S-20 and S-21). Even in patients who did not lose weight (those whose weight remained ±2kg of baseline); blood pressure did not significantly increase (See Supplementary Figures S-22-S-23). Total sleep time and total arousals on polysomnography and liver function tests were unaffected by armodafinil (See Supplementary Table S-4).

DISCUSSION

This study addressed the common problem of managing patients who refuse conventional treatments for sleep apnea such as CPAP and mandibular advancement splints. We hypothesized that the combination of armodafinil and weight loss would improve driving task performance at six months compared with placebo. However, armodafinil did not improve this primary outcome. Nevertheless, armodafinil improved driving performance at three months, facilitated a dietary intervention program by increasing fat mass loss by 2.4kg, and increased activity levels measured by actigraphy.

Our primary outcome was powered on the expectation that armodafinil would reduce a time-on-task decrement over the 90 minutes of the driving task.(29) As shown in Figure 2, the most likely explanation for the differential results at three and six months would be the improvement in time-on-task performance in the placebo group rather than a decline in the effectiveness of armodafinil. This could be due to a practice effect with faster learning on armodafinil. It should be noted that performance in these patients is still on average around 2SD worse than healthy controls.(27) It is also possible that there were interindividual differences in response to armodafinil, as previous groups have shown that *COMT* and *DAT* gene polymorphisms may predict susceptibility or resistance to modafinil.(30, 31) The dose used in our trial was a standard 150mg dose with no up-titration beyond this. It is possible that a higher dose e.g. up to 250mg, which has been tested previously,(32) may have produced an effect at six months.

Neither modafinil nor armodafinil have previously been investigated adjunctive to a diet and exercise weight loss program. Modafinil has previously been observed to have a small weight loss side effect in OSA patients in a clinical trial.(18) The size of the weight loss effect that we have observed was similar to other adjunctive weight loss agents, such as orlistat.(33) Like other drugs affecting dopaminergic,(34) orexinergic(35) or histaminergic(36) pathways, modafinil/armodafinil may act directly by decreasing appetite. Alternatively armodafinil may increase spontaneous physical activity or increase adherence to a diet and exercise regime through the treatment of negative behaviours such as apathy.(37-39) In our trial armodafinil caused an increase in activity, which could partly explain the weight loss. Eating behaviours were not detectably different between drug and placebo groups. Evidence for weight loss causation can also be found in the placebo and extension phases where the weight loss effect dissipated after the drug was withdrawn. This promising weight

loss effect could however still be due to chance, as it was only one of the three pre-specified secondary outcomes. It should also be noted that the effect size associated with the fat-mass reduction was small, at *d*=0.25 which we were not powered to reliably detect.

SAFETY

There was a signal for increased SAEs and AEs leading to withdrawal and all other AEs on armodafinil over placebo. The most common side effects were headaches, nausea and dizziness which are already listed in the prescribing information.(17) While increased blood pressure is reported elsewhere(17) we found no worsening of blood pressure. Even in our patients who did not lose weight there was no increase in blood pressure on armodafinil. There was no indication of increased cardiovascular risk on the Framingham score nor any of its modifiable components on armodafinil in this trial (the longest of modafinil or armodafinil in OSA) in the context of a weight loss program. This may allay some fears about its safety, especially in the light of the removal of OSA as an approved indication in Europe.(40)

LIMITATIONS

The 130 patient recruitment target was not met despite telescreening over 1500 potential participants. Dropout may have further reduced our ability to detect the primary effect, however as the time-on-task effect spontaneously resolved at six months in the placebo group it appears that we would have still been unlikely to reach significance, even if our sample size increased. Our dropout rate was around 25% in this study, which is less than the 40% from general obesity trials(41) and similar to other randomized diet trials in OSA, few of which have continued as long as this trial.(42, 43)

Recruitment was limited to those patients weighing <130kg due to weight bearing limitations on the DXA scanner so the results cannot be generalized to severely obese patients. Our weight loss intervention had relatively modest effects and it is possible these patients may benefit from a more aggressive weight loss approach, such as one we have successfully piloted.(44) The Epworth score at baseline averaged around 10, which is only around 1SD higher than population estimates.(45, 46) It should be noted, however, that for our primary outcome the patients we recruited had substantial functional driving decrement, with most patients being more than 2SDs worse than the reference mean.(26)

The Actiwatch II used in this study to quantify physical activity has not been validated as a physical activity monitor and the estimated increase in caloric output from an increase in activity count is unclear. We did not have a measure of compliance with the diet and exercise program and our measure of eating behavior changes, the three factor eating questionnaire, is not designed to identify changes in appetite. While it appears that the weight loss effect on armodafinil is being driven by the increase in activity, it is possible that the drug also had an anorexic effect, but we may not have a sensitive method of capturing this.

CONCLUSION

This is the longest randomized trial of ar/modafinil in patients with OSA and the only trialin conjunction with a weight loss program.(32, 47-49) There are three core findings of clinical relevance to physicians. Firstly, unexpectedly armodafinil did not improve driving task performance at the primary endpoint of six months (although it did at three months). Secondly, armodafinil might be a useful adjunctive to weight loss in OSA patients rejecting conventional treatments but this needs to be directly tested in a specifically designed, properly powered clinical trial. And finally, armodafinil appears safe to use in patients with OSA undergoing moderate weight loss. In particular, it does not seem to increase blood pressure. Research in this area needs to be continued with larger sample sizes, studies extended to at least 12 months, and adjunctive to more aggressive dietary programs. Future research may identify patients who are more responsive to armodafinil. Nevertheless, at this point in time there is not a clear rationale for armodafinil therapy in patients with sleep apnea not currently on CPAP.

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TABLE 1: CHARACTERISTICS OF RANDOMIZED PATIENTS BY DRUG AND DIET ALLOCATION

Legend: Values are mean (SD) unless otherwise noted. BMI – Body Mass Index, DXA- Dual-emission X-Ray Absorptiometry, AGHE – Australian Guide to Healthy Eating, LGHP- Low GI High Protein. The same patients are shown, first split by their drug allocation then by their diet allocation. The total number of patients enrolled was 113.

	DRUG ALLOCATION		DIET ALLOCATION		
Characteristic	**Placebo n=58**	**Armodafinil n=55**	**AGHE N=58**	**LGHP n=55**	**Whole group n=113**
Gender - n (%) female	12 (21%)	12 (22%)	10(17%)	14(25%)	24 (21%)
Age (years)	50.4(11.53)	51.7(10.81)	50.8(10.88)	51.2(11.53)	51.0(11.15)
Weight (kg)	101.8(13.33)	102.6(15.35)	103.9(14.25)	100.5(14.25)	102.2(14.29)
BMI (kg/m^2)	33.6(4.64)	34.1(4.51)	34.2(4.82)	33.5(4.29)	33.9(4.56)
DXA total body fat (kg)	3.86(9.12)	3.92(1.04)	3.91(1.04)	3.874(9.0)	3.89(9.71)
Neck circumference (cm)	41.8(3.34)	41.2(3.86)	42.1(3.65)	40.9(3.48)	41.5(3.6)
Waist circumference (cm)	108.8(8.98)	109.2(10.33)	110.2(10.16)	107.7(8.93)	109.0(9.62)
Systolic blood pressure (mmHg)	124.8(9.84)	129.6(13.28)	128.6(11.65)	125.6(11.94)	127.1(11.84)
Diastolic blood pressure (mmHg)	83.3(7.1)	85.2(8.87)	85.1(7.55)	83.3(8.49)	84.2(8.03)
Heart rate (beats/minute)	73.2(9.68)	71.4(9.07)	71.7(9.02)	73(9.8)	72.3(9.39)
Total sleep time (h)	6.4(0.78)	6.3(0.85)	6.5(0.77)	6.2(0.85)	6.4(0.81)
Arousal Index (/h)	32.5(17.37)	32.2(14.56)	32.2(14.84)	32.6(17.27)	32.4(16)
Apnea Hypopnea Index (/h)	43.1(24.19)	43.3(22.55)	42(22.34)	44.5(24.41)	43.2(23.31)
Oxygen disturbance (>3%) index (/h)	33.7(23.23)	30.5(19.49)	31.3(20.88)	33.1(22.23)	32.2(21.48)
Minimum SpO2 (%)	77.9(13.55)	79.7(12.29)	80.0(7.84)	77.5(16.65)	78.8(12.93)
SpO2 <90% (% of time in bed)	10.0(16.81)	4.7(4.74)	7.4(14.07)	7.5(11.37)	7.4(12.76)
Epworth Sleepiness Scale (/24)	10.2(4.54)	9.3(4.2)	9.7(4.18)	9.8(4.62)	9.7(4.38)
Functional Outcomes of Sleep Questionnaire (/120)	88.0(12.72)	91.8(15.07)	89.8(14.68)	89.9(13.3)	89.9(13.97)
Medical history					
Diabetes type II (n(%))	4 (6.9)	8 (14.5)	8 (13.8)	4 (7.3)	12 (10.6)
Coronary artery disease	3 (5.2)	3 (5.5)	4 (6.9)	2 (3.6)	6 (5.3)

TABLE 2: OUTCOMES MEASURED IN THE DRUG TRIAL

		Placebo			Armodafinil			Net effect 3 months	Effect size	p	Net effect 6 months	Effect size	p
		Baseline	3 months	6 months	Baseline	3 months	6 months						
Primary outcome	AusED steering deviation (cm)	62.9 (3.1)	68.6 (3.1)*	59.3 (3.1)*	61.2 (3.1)	57.9 (3.1)*	56.5 (3.1)*	12.9(4.1 to 21.7)	0.52	**0.0042**	5.5(-3.3 to 14.3)	0.22	0.2232
Secondary outcomes	Total fat (g)	38647 (1347)	.	35342 (1384)*	39180 (1383)	.	33302 (1412)*	.	.	.	2446(907 to 3984)	0.25	**0.002**
	Epworth score (/24)	10.2 (0.6)	8.5 (0.6)*	8.4 (0.6)*	9.3 (0.6)	8 (0.6)*	7.4 (0.6)*	-0.1(-1.4 to 1.2)	-0.03	0.847	0.2(-1.1 to 1.5)	0.05	0.729
	FOSQ total score (/120)	88 (1.9)	92.2 (2.1)*	94.4 (2.1)*	91.9 (2)	98 (2.1)*	101.5 (2.1)*	2.9(-1.7 to 7.5)	0.21	0.221	4.2(-0.5 to 8.9)	0.3	0.08
Tertiary outcomes	PVT reciprocal reaction time (1/ms)	3.94 (0.07)	3.89 (0.07)	3.92 (0.07)	3.83 (0.07)	3.89 (0.07)	3.93 (0.07)	0.1(-0.1 to 0.2)	0.17	0.225	0.1(0 to 0.2)	0.19	0.176
	n-back (% correct)	.	.	.	.	.	.	4.4(0 to 8.8)	.	0.051	-0.3(-4.7 to 4.2)	.	0.909
	Systolic blood pressure (mmHg)	124.8 (1.5)	120.8 (1.8)*	122.9 (1.7)	129.6 (1.5)	127.4 (1.7)	125.4 (1.7)*	-3.1(-6.8 to 0.7)	-0.26	0.109	1.6(-2.1 to 5.2)	0.13	0.398
	Diastolic blood pressure (mmHg)	83.3 (1)	79.9 (1.3)*	78.8 (1.2)*	85.2 (1.1)	82.2 (1.2)*	80.9 (1.2)*	-1.2(-4.2 to 1.7)	-0.15	0.417	-1(-3.7 to 1.8)	-0.12	0.5
	Framingham 10 year risk (%)	11 (1.1)	8.8 (1.2)*	10.4 (1.1)	13.1 (1.1)	11.8 (1.2)*	11.4 (1.2)*	-0.8(-2.4 to 0.7)	-0.09	0.298	1(-0.4 to 2.5)	0.12	0.175
	LDL Cholesterol (mmol/L)	3.2 (0.1)	2.9 (0.1)*	3.1 (0.1)	3.1 (0.1)	2.9 (0.1)	2.9 (0.1)	-0.16(-0.35 to 0.02)	-0.18	0.088	0.08(-0.11 to 0.27)	0.09	0.4
	HDL Cholesterol (mmol/L)	1.2 (0)	1.2 (0)	1.2 (0)	1.2 (0)	1.2 (0)*	1.3 (0)*	0.04(-0.02 to 0.1)	0	0.152	0.04(-0.01 to 0.1)	0	0.14
	Triglycerides (mmol/L)	1.9 (0.2)	1.6 (0.2)*	1.7 (0.2)	1.6 (0.2)*	1.5 (0.2)*	1.7 (0.2)	-0.1(-0.4 to 0.3)	-0.07	0.64	-0.2(-0.6 to 0.1)	-0.21	0.19
	HbA1c NGSP (%)	5.5 (0.2)	5.7 (0.4)	5.6 (0.3)	5.8 (0.2)	5.5 (0.4)	5.5 (0.3)	0.6(-0.1 to 1.3)	0.52	0.112	0.7(-0.1 to 1.4)	0.6	0.068
	HOMA-IR (UNIT)	5.5 (1)	5.1 (1.1)	4.6 (1.1)	7 (1)	6 (1.1)	5.5 (1.1)	1(-1.1 to 3.2)	0.03	0.347	0.4(-1.7 to 2.6)	0.01	0.677
	Daily activity (count/24hours)	263952 (11664)	291168 (12816)*	287280 (13104)	267840 (12240)	312192 (13248)*	314640 (13680)*	19152(-7920 to 46080)	0.27	0.166	28800(576 to 57024)	0.4	**0.045**
Post hoc outcomes	Weight (kg)	101.8 (1.9)	99 (1.9)*	98.2 (1.9)*	102.6 (2)	96.7 (2)*	96 (2)*	3(1.1 to 4.9)	0.21	**0.002**	2.9(0.9 to 4.8)	0.2	**0.004**
	Apnea hypopnea index (/h)	43.1 (2.9)	.	38.7 (3.2)	43.3 (3)	.	34.2 (3.2)*	.	.	.	3.9(-1.4 to 9.2)	0.17	0.144

Legend: Values for Baseline, 3 and 6 months are least square means (standard error). Values for the net effect are the difference of least square means for the change from baseline and 95% confidence limits. Positive numbers here denote that armodafinil outperformed placebo. Due to collection error mean scores for n-back are not collated here but the change scores are reported. DXA – dual-emission x-ray absorptiometry, FOSQ – Functional Outcomes of Sleep Questionnaire, PVT – psychomotor vigilance task , SF36 – Short form 36 quality of life questionnaire LDL – Low-density lipoprotein, HDL- High-density lipoprotein, HbA1c NGSP – glycated hemoglobin (National Glycohemoglobin Standardization Program), HOMA- Homeostatic model assessment.

TABLE 3: MOST COMMON ADVERSE EVENTS SUFFERED DURING THE DRUG TRIAL (SUFFERED BY ≥5% OF PATIENTS)

MedDRA Preferred Term	Armodafinil	Placebo
Headache	15	5
Nausea	12	2
Dizziness	11	2
Influenza like illness	7	2
Influenza	2	5
Insomnia	6	2
Initial insomnia	3	5
Cough	5	3
Nasopharyngitis	4	7
Oropharyngeal pain	1	5

LEGEND: NUMBERS ARE FREQUENCY OF EACH EVENT IN EACH GROUP. NOTE: EVENT MAY HAVE OCCURRED MORE THAN ONCE FOR EACH PATIENT. MEDDRA: MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES.

FIGURE 1: FLOW CHART OF PATIENTS THROUGH THE STUDY

LEGEND: * SEE ONLINE SUPPLEMENTARY MATERIAL FOR REASONS PARTICIPANTS WERE INELIGIBLE, WITHDREW OR CEASED STUDY MEDICATION THROUGHOUT THE STUDY. CPAP- CONTINUOUS POSITIVE AIRWAY PRESSURE, MAS – MANDIBULAR ADVANCEMENT SPLINT, OSA – OBSTRUCTIVE SLEEP APNEA, DXA – DUAL-EMISSION X-RAY ABSORPTIOMETRY, AUSED – DRIVING TASK

FIGURE 2: SIMULATED STEERING DEVIATION ACROSS THE 90 MINUTE DRIVE AT THE BASELINE, 3 MONTH AND 6MONTH VISITS

LEGEND: EACH BIN REPRESENTS A 5 MINUTE PERIOD. BIN NUMBER 1 IS EXCLUDED TO ENABLE PARTICIPANTS TO ACCUSTOMIZE TO THE DRIVE. ERROR BARS REPRESENT 95% CONFIDENCE LIMITS. THE DASHED LINE AT 54.6CM REPRESENTS THE 2SD ABOVE NORMAL CUT-OFF USED TO DEFINE ABNORMAL STEERING DEVIATION FROM VAKULIN ET AL 2014. DISPLAYED P VALUE BELOW EACH FIGURE DENOTES THE BETWEEN GROUP DIFFERENCE IN TIME-ON-TASK DECREMENT OVER THE FULL 90 MINUTES AT THAT VISIT. THE P VALUES TO THE RIGHT REPRESENT THE DIFFERENCE BETWEEN THE GROUPS IN CHANGE FROM BASELINE FOR THE FINAL 30 MINUTES AT THAT VISIT (PRIMARY HYPOTHESIS).

FIGURE 3 DUAL-EMISSION X-RAY ABSORPTIOMETRY (DXA) TOTAL FAT MASS BY DRUG ALLOCATION

LEGEND: THIS GRAPH SHOWS THE FAT MASS PLOTTED AT EACH TIMEPOINT FOR EACH OF THE GROUPS AND 95% CONFIDENCE LIMITS.THERE WAS A SIGNIFICANT DIFFERENCE BETWEEN THE GROUPS AT THE 6 MONTH VISIT. AT 12 MONTHS AND AFTER 6 MONTHS OF FOLLOW-UP OFF DRUG, THERE WAS NO LONGER ANY DIFFERENCE BETWEEN THE GROUPS.