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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.

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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

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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)

Funding Source

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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

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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.

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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

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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

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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).

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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).

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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)

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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

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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).

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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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Psychiatry. 2011 Aug;72(8):1157 Note: Yang, Ronghua R [corrected to Yang, Ronghua]]. *J Clin Psych* 2010; 71: 32-40.

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

	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(%))** **Coronary artery disease**	 4 (6.9) 3 (5.2)	 8 (14.5) 3 (5.5)	 8 (13.8) 4 (6.9)	 4 (7.3) 2 (3.6)	 12 (10.6) 6 (5.3)

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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.

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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.

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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.

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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.

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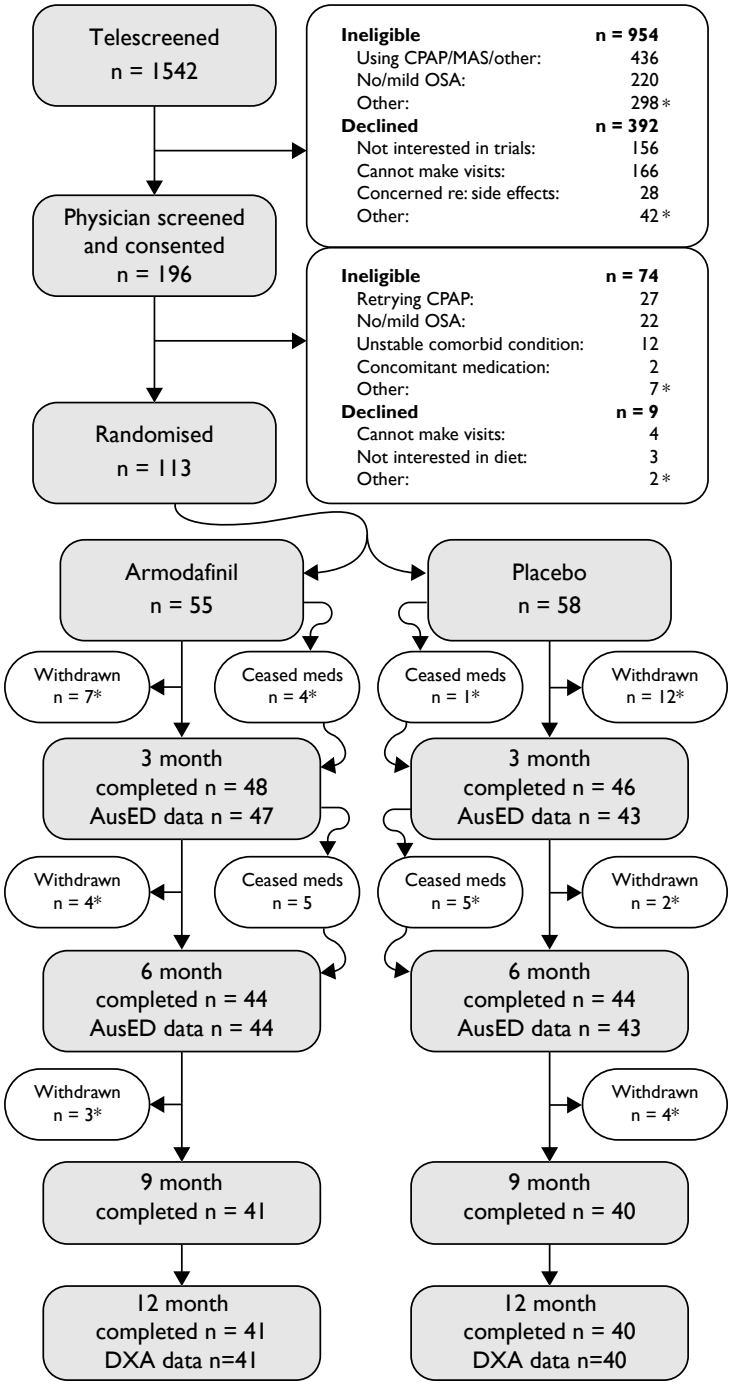

Figure 1

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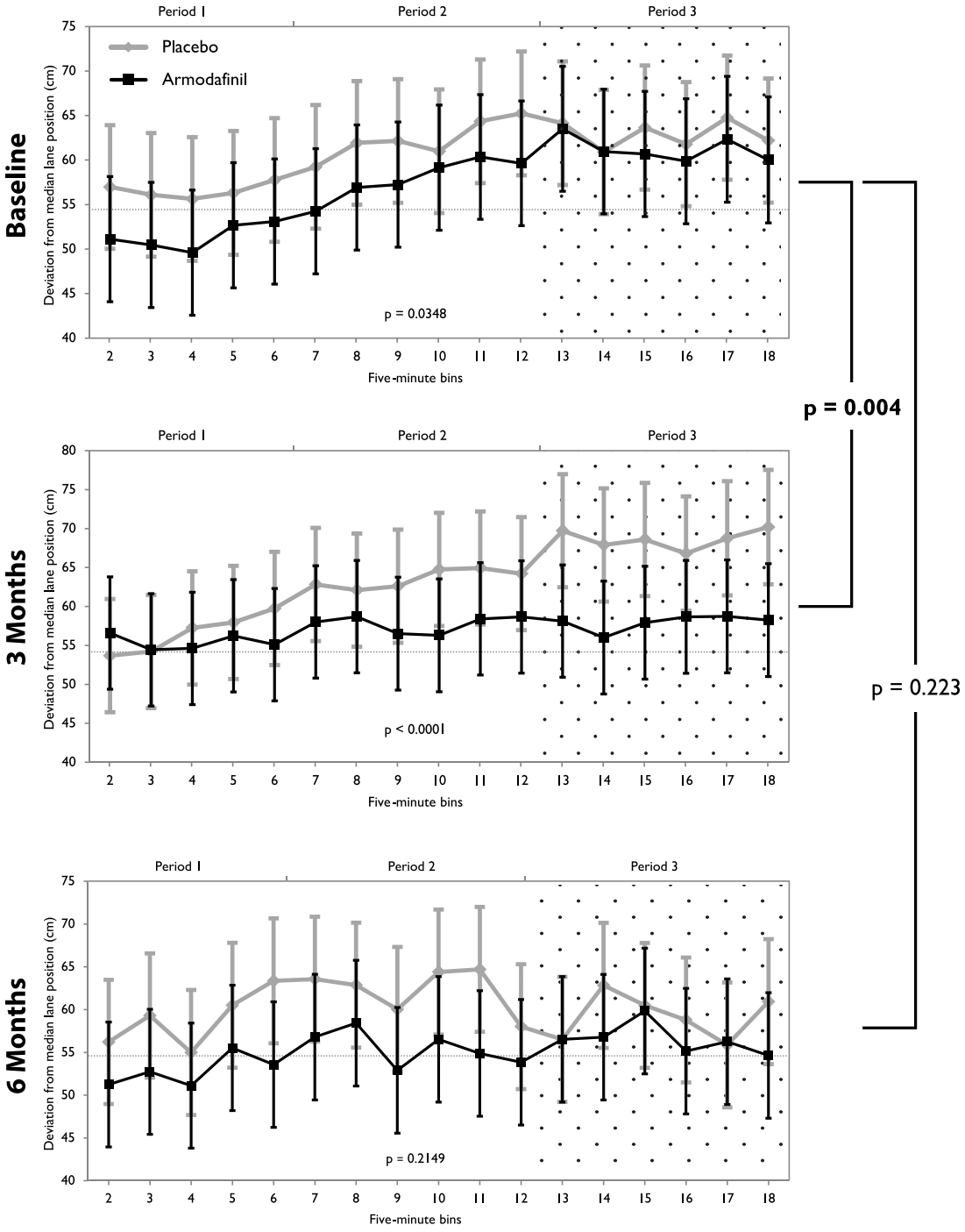

Figure 2

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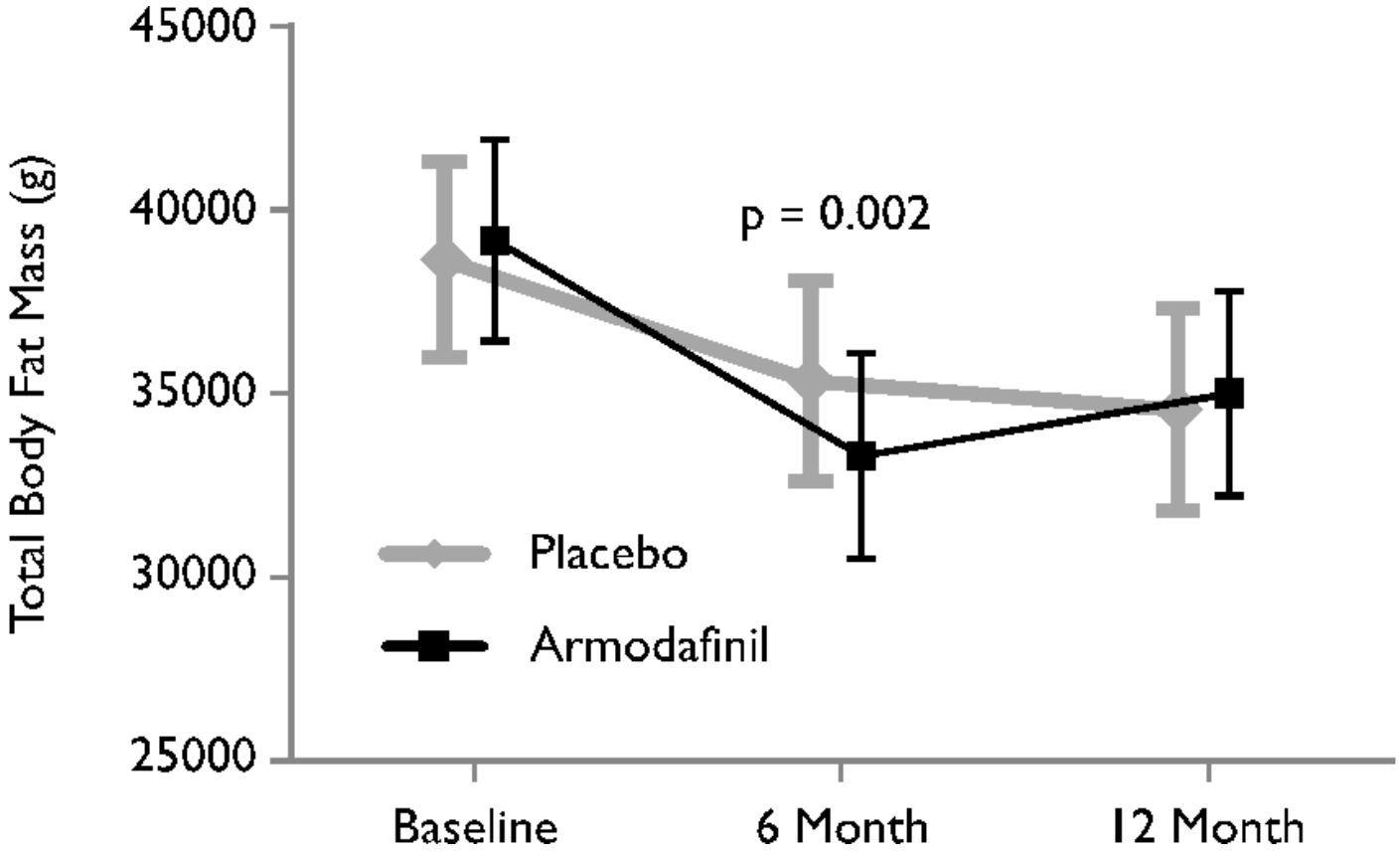

Figure 3

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Supplementary Methods

Complete Inclusion and Exclusion Criteria from the protocol

Inclusion
1. Males & Females aged 18-70 years.
2. General or central obesity. BMI:≥27 but less than 40kg/m^2 or waist circumference ≥80cm for women and ≥94cm for men.
3. Moderate-severe and symptomatic OSA (Apnea Hypopnea Index (AHI) ≥ 15/hr with concomitant daytime sleepiness ESS≥10 or clinical report of disturbing daytime sleepiness).
4. Ambulatory and community-dwelling.
5. Hold a current drivers license.
6. Must have rejected CPAP and MAS within the past 2 years. Otherwise patients will be encouraged to recommence a standard mechanical treatment.
Exclusion
1. Pregnancy or lactation- the effects of this drug on pregnant women or their unborn children is unknown and the obesity reduction program is NOT suitable for pregnant or lactating women. CAUTION: Fertile women should be warned that this class of medication is known to interfere with contraceptive pills and they should employ additional contraceptive strategies.
2. Severe hypertension (SBP≥180 and/or DBP≥110).
3. Patients with moderate-severe skin allergies and/or eczema should not be enrolled due to side effects of this drug class being reported in these patients.
4. Shift workers who rotate to night shift.
5. Unstable Angina / Heart Failure (NYHA Class III and IV)/ Stroke.
6. Current use of device based treatment (CPAP, MAS or positional treatment) OR upper airway surgery with 6 months.
7. Cognitive impairment / Psychiatric disorder / Physically unable to participate.
8. Severe OSA (minimum oxygen saturation < 65% or RDI > 100) or excessively sleepy patients at increased risk for driving-related accidents requiring immediate treatment.
9. More than 20% of AHI with central apneas.
10. Previous use of Modafinil or Armodafinil
11. Alcohol or Caffeine dependence as patients undergo multiple 24 hours periods in our sleep laboratory without access to these.
12. Cytochrome P450 affecting drugs
13. Patients with severe tonsillar enlargement or nasal obstruction will be referred to an ENT surgeon for surgical intervention before an additional attempt at CPAP or MAS use.
14. Severe Haemophobics as we must take blood as a safety check in this study.
15. Participation in a drug trial or lifestyle modification program within the preceding three months.

Randomization and allocation concealment

The randomization sequences were generated electronically by an unblinded statistician who had no role in patient selection or follow-up. The randomization was based on a 2x2 factorial design. Block

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randomization was applied with block sizes of 12 or 16. Randomization lists were also stratified at the cut-line between class 1 and 2 obesity (Class1<BMI35kg/m2<Class2) to ensure that there were equal numbers of moderately and more severely obese patients on each diet and each drug. Patients were randomized in a 1:1 ratio to armodafinil (3X50mg tablets: morning) or placebo (3 tablets, shape, colour and taste-matched) for 6 months and then a 3 month run out with all patients on placebo. Patients were concurrently randomized in a 1:1 ratio to either a standard hypocaloric diet based on the Australia Guide to Healthy Eating (AGHE) or a hypocaloric diet with a focus on Low GI and High Protein (LGHP) foods. All randomized patients were also provided with exercise advice.

A pre-printed randomization log, which simply listed the randomization numbers without allocation was located in the Woolcock Institute pharmacy. When it came time to randomize a patient, the next number off the list was chosen for that patient for their obesity class (Class 1 or 2) and the patient's initials were listed next to that randomization number. If a patient withdrew at any time after that point, their randomization number was not reused and they were assumed enrolled in the study for analysis purposes.

Armodafinil and matching placebo were dispensed into randomization coded bottles (six per patient, two to be dispensed at each of the baseline, three and six month visits) by two unblinded pharmacists at the Woolcock Institute of Medical Research. Study doctors, study coordinators, dietitians, research assistants and outcomes assessors were blinded to treatment allocation throughout the duration of the drug trial. At the baseline, three and six month visits, 276 x 50mg or matching placebo tablets were dispensed. If a patient was unable to attend one of these visits within the required timeframe and required extra medication, emergency resupply bottles were available (containing 42 tablets). To obtain these, the study coordinator emailed the unblinded pharmacist to request an appropriate emergency resupply bottle for that patient and this was recorded on the pharmacy dispensing log.

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After the diet allocation envelope was opened the diet allocation was known by the study coordinator, dietitians and the patient so that the patient may follow the correct diet allocated to them. The investigator (CH) who scored and exported the DXA scan data (primary outcome of the diet trial) was blinded to diet allocation and had no contact with the study participants.

Treatments

Patients experiencing adverse events were advised by a study physician to cease or reduce their dose before increasing back to three tablets per day if they were able. Adherence with study medication was assessed by counting returned tablets at each three-monthly visit or by patient report of complete course.

All patients were given exercise advice in accordance with the American College of Sports Medicines' recommendations for reducing overweight and obesity (250 minutes of aerobic exercise and two structured resistance training sessions per week).(50) Individual patients' energy requirements were calculated using the Harris-Benedict Equation and appropriate activity factor with a 500 calorie deficit applied to promote 0.5kg of weight loss per week.(51) The major difference between the diets was that patients allocated to the LGHP group were given a "shopper's guide" book to help determine the glycemic index of foods, which they were educated about during their sessions with the dietitian.(52)

Study procedures and measurements

Patients were initially contacted via telephone or email by a study coordinator, were asked general screening questions such as whether they matched age, weight and OSA treatment requirements, and were provided with the participant information sheet. If they passed this initial telescreening, participants were then invited to attend a screening and consent visit with one of the study physicians and a study coordinator, where inclusion criteria were fully assessed after signed

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informed consent had been obtained. The pharmacogenetic sub-study (for assessment of COMT polymorphism) had an additional consent form, which they were given time to read and were then asked to sign with a study coordinator or study physician if they agreed to the sub-study. Their participation in the main study was not affected by their decision to enrol or not enrol in the sub-study.

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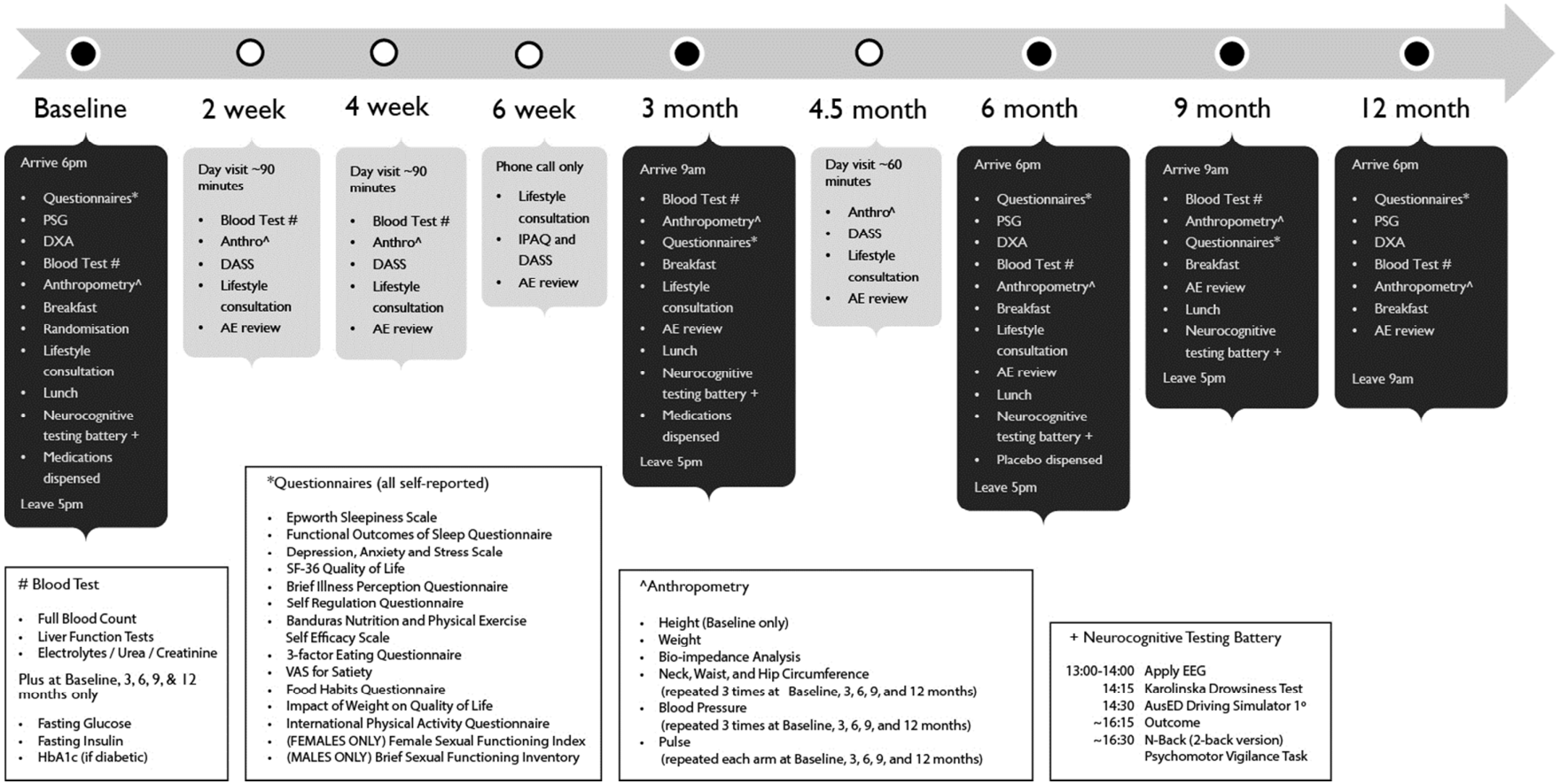
Figure S- 1: Overview of study procedures



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Description of tests

To capture the time-on-task decrement during the AusED driving task, the standard deviation (SD) in lane position was averaged in 5 minute 'bins' across the 90 minute drive with the first bin discarded due to drivers calibrating steering wheel sensitivity. (53) (53)

Tertiary outcomes included: working memory (percent correct on the visual n-back (2-back version),(54) reaction time on the ten-minute Psychomotor Vigilance Task (PVT),(55) Framingham 10-year Cardiovascular Risk,(56) Homeostatic Model Assessment for Insulin Resistance,(57) glycated hemoglobin (HbA1c), low and high density lipoprotein (LDL, HDL), triglycerides, blood pressure and daily activity counts (measured using wrist actigraphy (Philips Actiwatch II)). The Three Factor Eating Questionnaire (3FEQ) was administered to assess changes in eating behaviors.(58)

The n-back is a four minute computerized memory task where participants monitor a series of stimuli (in this case letters appearing at different locations on the computer screen) and respond when a stimulus is presented that is the same as the one presented "n" times previously. In this case the participant must press a button on the computer keyboard if the letter that appears on the screen is in the same location as the one two times previously. The number of correct responses is then recorded as the unit of analysis. We noticed after the commencement of data collection that there was an error whereby around a third of patients were given incorrect instructions for the n-back at baseline. These patients were instructed to match a set of four letter locations (letter 3 to letter 1 and letter 4 to letter 2) then start again. The correct instructions are to continue matching with no gaps (i.e. match letter 3 to letter 1, letter 4 to letter 2, letter 5 to letter 3 and so on). As patients were given the correct or incorrect instructions at baseline they were asked at subsequent visits to continue performing the n-back as per the instructions given at baseline, so within individual improvements in number correct should be consistent, but between individual comparisons may be

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problematic. So I have collated here the difference between the groups in *change* in number correct, but will not attempt to collate this at the group level.

Polysomnography

Overnight polysomnography was scored using the American Academy of Sleep Medicine Scoring manual 2012.(59) The definition of each of the events is as below:

Apnea: Complete cessation of airflow for ≥10 sec, measured via pressure transducer and a reduction by ≥90% via a thermister.

Hypopnea: Reduction in airflow ≥30% for ≥10 sec, measured via pressure transducer, with either an arousal or ≥3% desaturation.

RERA: Increased respiratory effort OR flattening of airflow for ≥10 sec leading to an arousal. Included in total arousal index.

Apnea Hypopnea Index: Includes: Apneas and hypopneas. Does not include RERAs.

Respiratory Disturbance Index: Apneas, hypopneas and RERAs.

Actigraphy

All participants were asked to wear an actiwatch (Phillips Actiwatch 2), on their non-dominant wrist for seven days in the lead up to their baseline, 3, 6, 9 and 12 month visits. Actigraphy was recorded in 30 second epochs. Actigraphy was processed using Phillips Actiware V 6.0.2, with in-bed times manually corrected, and actiwatch time off-wrist excluded from the analysis. Activity counts were reported per minute for both the in-bed and wake periods. Activity count across the 24 hour period was used to compare activity before and after treatment, and between groups.(60)

Safety measurements

Adverse event reports were collected spontaneously and at each visit by asking patients if they had noticed any changes since their last visit or visited a doctor or hospital.

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After study completion, adverse events were coded by a study physician and coordinator using the Medical Dictionary for Regulatory Activities (MedDRA).(61) A *Lowest Level Term* was selected which best matched the symptom recorded by study coordinator or study physician in the patient's notes. The corresponding *Preferred Terms* were used for quantification and analysis of adverse events. Adverse events are reported for all randomized participants. Serious adverse events were defined as any event resulting in death, hospitalization or prolongation of hospitalization or was immediately life threatening.

For blood pressure, at the major visits (Baseline, 3 and 6 months), one measurement was taken for each arm and 1-2 minutes rest was allowed between each measurement.(62) A third measure was taken from the higher arm if there was more than 10 mmHg discrepancy between the first two measurements. A mean of the two higher measurements was calculated for data analysis. Heart rate was measured using manual palpation of the radial artery. Patients also completed the depression, anxiety and stress scale (DASS) questionnaire at each visit to monitor any adverse mood changes.(63)

Genotype analysis

A circadian biochemist (Author MC) genotyped patients using genomic DNA which was extracted from buffy coat and DNA fragments containing the Val158Met polymorphism were amplified and then digested with NlaIII to obtain the bands that discern between the different genotypes. (64, 65)

Statistical analyses

Study data was collated in online case report forms (Research Tools™) and Statistical analyses performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) using mixed model analysis of variance.

Data from the AusED driving simulator was reported in 18 five minute bins across the 90 minutes of the drive. The final six bins were specifically interrogated for the primary analysis (steering deviation in the final 30 minutes). Change from baseline to end-of-treatment in continuous variables (AusED steering deviation, ESS, FOSQ and PVT reciprocals of reaction times) were analysed using mixed

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model analysis of variance (PROC MIXED in the SAS 9.4 program) classifying all randomized patients as random factors and treatment and time as a fixed factor using a time by treatment interaction to test for specific differences at three and six month visits. For the primary outcome of steering deviation, the mixed models classified patients as random factors and treatments (armodafinil vs placebo), visit (0,3,6 & 9 months) and period (6-30, 31-60 & 61-90 minutes) as fixed factors with an interaction between treatment, visit and period specifically in the last 30 minutes. In order to draw Figure 2 we re-ran this model using period classified in 5-minute bins instead of 30-minute bins. We did not impute missing data in any patient but included them in the mixed model and allowed the model to integrate their data into the overall estimates. Mixed models require the residual values to be normally distributed. We plotted the residuals for each model in histograms and QQ plots to visually confirm tolerable normality.

Pearson's correlations were performed for linear relationships. Relative risk was calculated for the likelihood of adverse events. Effect sizes (Cohen's d) were calculated by dividing the placebo-adjusted effect by the SD of that measure at baseline.(66)

All patients were analysed in the group they were randomized to as per the intention-to-treat principle.(67) An additional per-protocol analysis was performed assessing the effect of adherence with study medication. No interim data analyses were undertaken.

The per-protocol analyses reported here are for primary (steering deviation from the final 30 minutes of the AusED driving simulator) and secondary outcomes (ESS score, FOSQ score and DXA-measured total fat mass) only. For the AusED driving simulator it is expected that performance would most likely be acutely affected by medication on the day of testing so the per-protocol analysis includes only those participants who took study medication on the morning of the testing

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visit. For measures which may be affected by regular chronic use of the medication, such as the Epworth, FOSQ and fat loss, the number of tablets taken over the past three months was used as an indicator of adherence. A histogram of number of tablets returned was created and based upon this participants were split into quartiles of adherence to enable analysis to compare those with poor to high adherence and whether this had an effect on outcomes. As all participants in this study were on a weight loss program, in order to determine the effect on blood pressure within those patients who did not lose weight, an analysis was performed on the subgroup of patients who had no weight change (that is weight was +/-2kg of weight at baseline).

The a-priori power calculation showed that 130 patients were required to detect a 6cm difference in improvement in steering deviation on a background of 11.3cmSD(53) with Alpha=0.05, Power=0.8. Similarly, 116 patients were required to show equivalence with a 0.55SD margin in fat mass loss with Alpha=0.05, Power=0.8. A 0.55SD margin equates to ±3.3kg equivalence margin in a 100kg person with 33% fat mass.(68)

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Supplementary Results

Figure S- 2: Reasons Participants were Ineligible after Telescreening

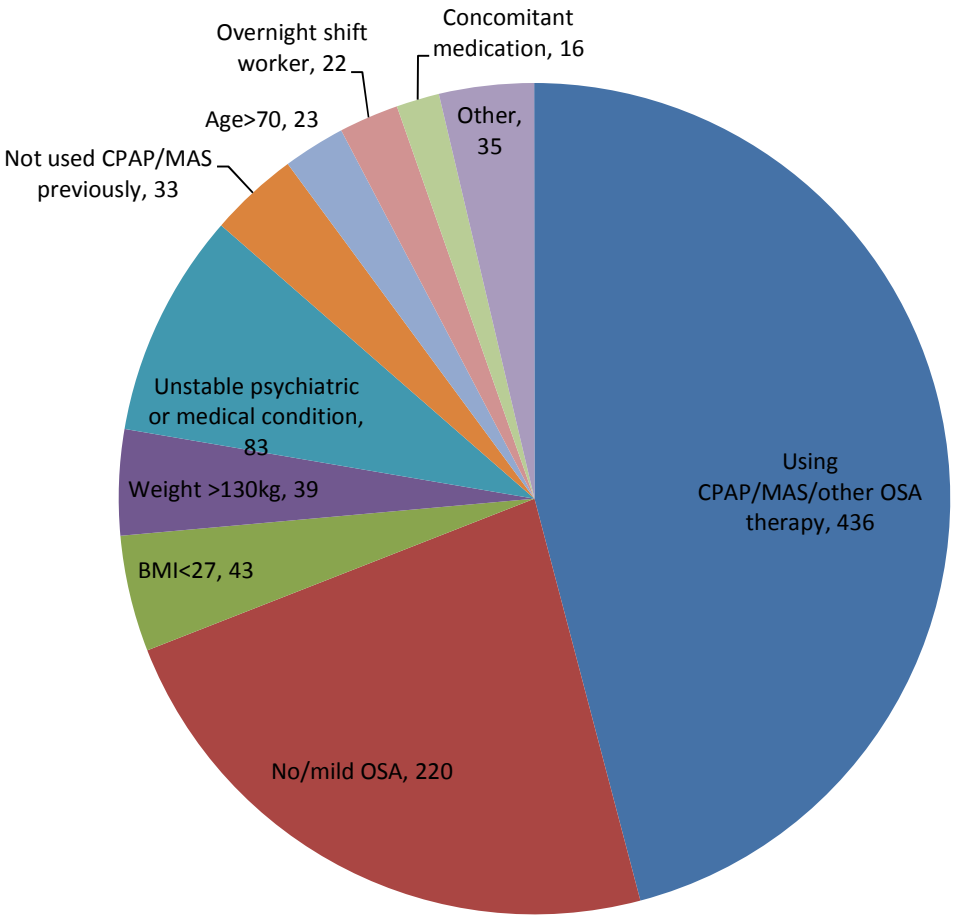

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Figure S- 3: Reasons Participants Declined after Telescreening

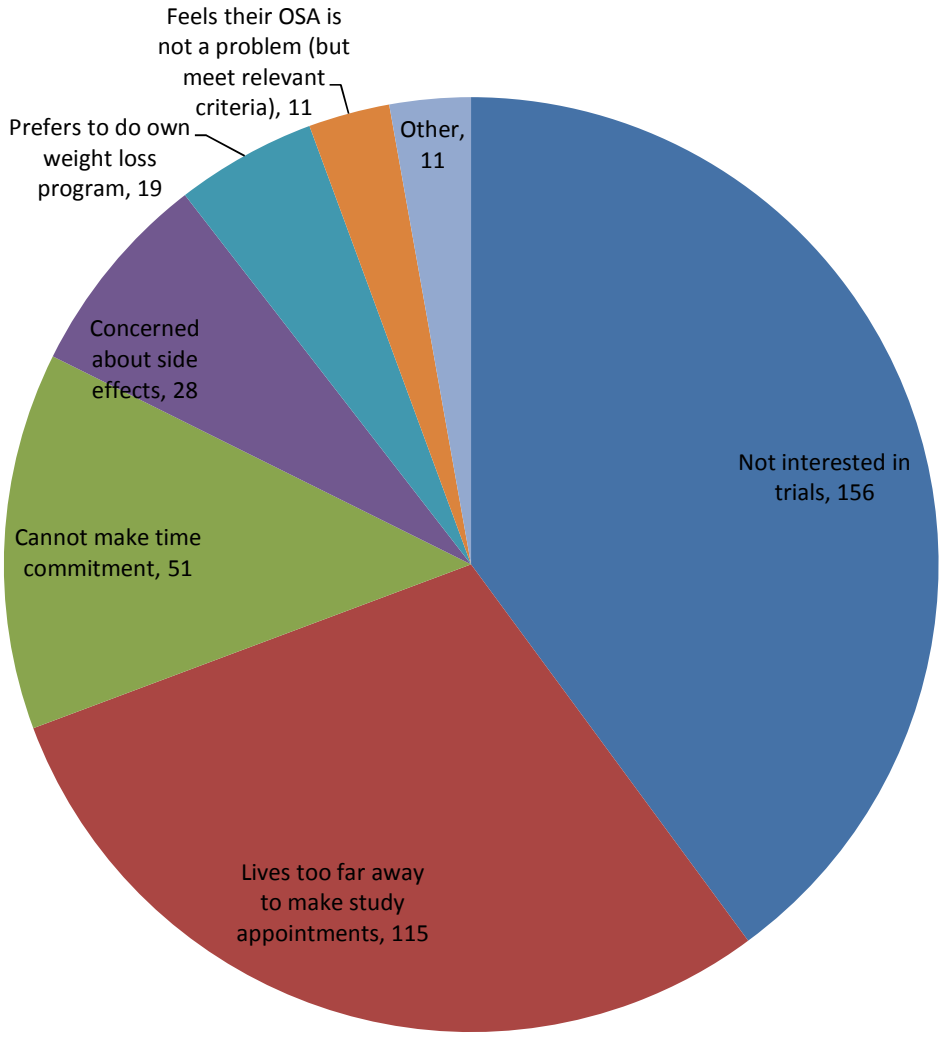

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Table S- 1: List of reasons participants were ineligible after physician screening
Legend: OSA – Obstructive Sleep Apnea, ENT – Ear, nose, and throat surgeon, EDS – Excessive daytime sleepiness, CPAP – Continuous positive airway pressure.

Screening Number	Reason ineligible listed in flow chart	Specific reason ineligible
S076	Comorbid condition	Comorbid condition (bowel cancer)
S060	Comorbid condition	Comorbid condition (cardiac)
S064	Comorbid condition	Comorbid condition (cardiac)
S077	Comorbid condition	Comorbid condition (cardiac)
S103	Comorbid condition	Comorbid condition (cardiac)
S149	Comorbid condition	Comorbid condition (cardiac)
S129	Comorbid condition	Comorbid condition (prostate cancer)
S160	Comorbid condition	Comorbid condition (prostate cancer)
S115	Comorbid condition	Comorbid condition (psychiatric)
S119	Comorbid condition	Comorbid condition (psychiatric)
S183	Comorbid condition	Comorbid condition (psychiatric)
S188	Comorbid condition	Comorbid condition (psychiatric)
S024	Concomitant medication	Concomitant medication
S071	Concomitant medication	Concomitant medication
S010	No/mild OSA	No/mild OSA
S018	No/mild OSA	No/mild OSA
S028	No/mild OSA	No/mild OSA
S037	No/mild OSA	No/mild OSA
S048	No/mild OSA	No/mild OSA
S050	No/mild OSA	No/mild OSA
S053	No/mild OSA	No/mild OSA
S059	No/mild OSA	No/mild OSA
S062	No/mild OSA	No/mild OSA
S063	No/mild OSA	No/mild OSA
S090	No/mild OSA	No/mild OSA
S099	No/mild OSA	No/mild OSA
S109	No/mild OSA	No/mild OSA
S111	No/mild OSA	No/mild OSA
S136	No/mild OSA	No/mild OSA
S140	No/mild OSA	No/mild OSA
S141	No/mild OSA	No/mild OSA
S157	No/mild OSA	No/mild OSA
S161	No/mild OSA	No/mild OSA
S165	No/mild OSA	No/mild OSA

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Screening Number	Reason ineligible listed in flow chart	Specific reason ineligible
S182	No/mild OSA	No/mild OSA
S192	No/mild OSA	No/mild OSA
S113	Other	Already undertaking diet and exercise program
S151	Other	Already undertaking diet and exercise program
S108	Other	Massive tonsils referred to ENT for surgery
S069	Other	Nil EDS
S096	Other	No OSA, Narcolepsy
S073	Other	Not overweight
S169	Other	Planned surgery (knee replacement)
S004	Retrying CPAP	Retrying CPAP
S016	Retrying CPAP	Retrying CPAP
S019	Retrying CPAP	Retrying CPAP
S025	Retrying CPAP	Retrying CPAP
S026	Retrying CPAP	Retrying CPAP
S032	Retrying CPAP	Retrying CPAP
S054	Retrying CPAP	Retrying CPAP
S065	Retrying CPAP	Retrying CPAP
S078	Retrying CPAP	Retrying CPAP
S081	Retrying CPAP	Retrying CPAP
S084	Retrying CPAP	Retrying CPAP
S087	Retrying CPAP	Retrying CPAP
S102	Retrying CPAP	Retrying CPAP
S105	Retrying CPAP	Retrying CPAP
S117	Retrying CPAP	Retrying CPAP
S134	Retrying CPAP	Retrying CPAP
S159	Retrying CPAP	Retrying CPAP
S166	Retrying CPAP	Retrying CPAP
S167	Retrying CPAP	Retrying CPAP
S168	Retrying CPAP	Retrying CPAP
S170	Retrying CPAP	Retrying CPAP
S171	Retrying CPAP	Retrying CPAP
S172	Retrying CPAP	Retrying CPAP
S178	Retrying CPAP	Retrying CPAP
S187	Retrying CPAP	Retrying CPAP
S191	Retrying CPAP	Retrying CPAP
S193	Retrying CPAP	Retrying CPAP
S162	Weighs >130kg	Weighs >130kg

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Screening Number	Reason ineligible listed in flow chart	Specific reason ineligible
S186	Weighs >130kg	Weighs >130kg
S152	Weighs >130kg	Weighs >130kg
S036	Weighs >130kg	Weight >130kg

Table S- 2: List of reasons participants declined after physician screening

Screening Number	Reason declined listed in flow chart	Specific reason declined
S042	Cannot make study visits	Cannot make study visits
S058	Cannot make study visits	Cannot make study visits
S130	Cannot make study visits	Cannot make study visits
S194	Cannot make study visits	Cannot make study visits
S023	Not interested in diet program	Not interested in diet program
S034	Not interested in diet program	Not interested in diet program
S035	Not interested in diet program	Not interested in diet program
S066	Other	Declined participation due to potential side effects of armodafinil
S145	Other	Declined as he wished to pursue an alternative clinic for his OSA management

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Reasons for Post-randomization Withdrawal from the Study or from Study Medication (split by drug allocation)

Armodafinil

Withdrawn prior to first dose:

- 1R063 Possible drug seeking behaviour

Ceased study medications prior to three month testing:

- 1R006 Adverse event - Pins and needles, tongue soreness, no features of SJS
- 1R012 Did not initiate medication due to illness starting day of baseline - headache, GORD flare up
- 2R009 Adverse event - Insomnia
- 2R025 Adverse event - Pre-syncopal episodes

Withdrawn prior to three month testing

- 1R048 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R064 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R021 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R024 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R027 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R037 Serious adverse event, diverticulitis and abnormal liver function tests

Ceased study medications prior to six month testing

- 1R013 Adverse event - Mood changes, anger, anxiety
- 1R037 Adverse event - Nausea and lightheadedness
- 1R065 Patient reported lack of efficacy
- 2R029 Adverse event - Nausea, dizziness, light-headedness, anxiety
- 2R041 Adverse event – Stress related temporomandibular joint dysfunction

Withdrawn prior to six month testing

- 1R006 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R062 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R007 Patient withdrew, unable and unwilling to make time for any further study visits

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- 2R010 Patient moved interstate unable to attend further visits

Withdrawn prior to nine month testing

- 1R027 Adverse event – giant cell arteritis
- 1R065 Patient withdrew, lack of efficacy
- 2R041 Lost to follow-up

Withdrawn prior to twelve month testing

- nil

Placebo

Withdrawn prior to first dose

- 2R039 Participant was unable to perform AusED driving simulator (primary outcome)

Ceased study medications prior to three month testing

- 1R025 Adverse event – insomnia

Withdrawn prior to three month testing

- 1R004 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R010 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R028 Diagnosed with underlying heart condition (from Baseline PSG), patient unwilling to continue visits without treatment
- 1R068 Patient moved interstate unable to attend further visits
- 1R069 Patient reported lack of efficacy
- 1R070 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R002 Lost to follow-up
- 2R012 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R020 Patient reported lack of efficacy
- 2R026 Serious adverse event - Hospitalization due to worsening of neuromuscular condition
- 2R038 Adverse event – Headache, depressed mood, anger

Ceased study medications prior to six month testing

- 1R035 Completed as exit visit after study medication ran out

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- 1R041 Completed as exit visit after study medication ran out
- 1R057 Did not initiate study medication (returned all tablets)
- 1R066 Adverse event – depressed mood
- 2R017 Completed as exit visit after study medication ran out

Withdrawn prior to six month testing

- 1R040 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R059 Patient withdrew – did not give a reason

Withdrawn prior to nine month testing

- 1R025 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R066 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R013 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R033 Patient withdrew, unable and unwilling to make time for any further study visits

Withdrawn prior to twelve month testing

- nil

Reasons for Post-randomization Withdrawal from the Study (split by diet allocation)

LGHP

Withdrawn prior to first dose

- 1R063 Possible drug seeking behaviour
- 2R039 Participant was unable to perform AusED driving simulator (primary outcome)

Withdrawn prior to three month testing

- 1R028 Diagnosed with underlying heart condition (from Baseline PSG), patient unwilling to continue visits without treatment
- 1R068 Patient moved interstate unable to attend further visits
- 1R070 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R002 Lost to follow-up
- 2R012 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R020 Patient reported lack of efficacy

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Withdrawn prior to six month testing

- 1R006 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R040 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R062 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R010 Patient moved interstate unable to attend further visits

Withdrawn prior to nine month testing

- 1R027 Adverse event – giant cell arteritis
- 1R066 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R013 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R041 Lost to follow-up

AGHE

Withdrawn prior to three month testing

- 1R004 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R010 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R048 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R064 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R069 Patient reported lack of efficacy
- 2R021 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R024 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R026 Serious adverse event - Hospitalization due to worsening of neuromuscular condition
- 2R027 Patient withdrew, unable and unwilling to make time for any further study visits
- 2R037 Serious adverse event, diverticulitis and abnormal liver function tests
- 2R038 Adverse event – Headache, depressed mood, anger

Withdrawn prior to six month testing

- 1R059 Patient withdrew – did not give a reason
- 2R007 Patient withdrew, unable and unwilling to make time for any further study visits

Withdrawn prior to nine month testing

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- 1R025 Patient withdrew, unable and unwilling to make time for any further study visits
- 1R065 Patient withdrew, lack of efficacy
- 2R033 Patient withdrew, unable and unwilling to make time for any further study visits

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Medication compliance was able to be quantified for the 86 patients who returned study medication or reported that they threw away empty bottles at the six month visit. A histogram of the number of tablets returned can be seen in Figure S-5. Those with the lowest compliance returned 75 or more tablets (Compliance Quartile (CQ) 1), those with the next lowest compliance returned between 40 and 74 tablets (CQ2), those with the second best compliance (CQ3) returned between 1 and 39 tablets and the best compliance quartile (CQ4) returned no tablets.

Figure S- 4: Histogram of tablets returned at the 6 month visit.
Legend: Horizontal axis is number of tablets returned in categories centred around the numbers listed. Based upon this data, participants were split into quartiles of compliance. Median 40, interquartile range 1 to 74 for per protocol analyses of measures which may be affected by regular chronic use of the medication.

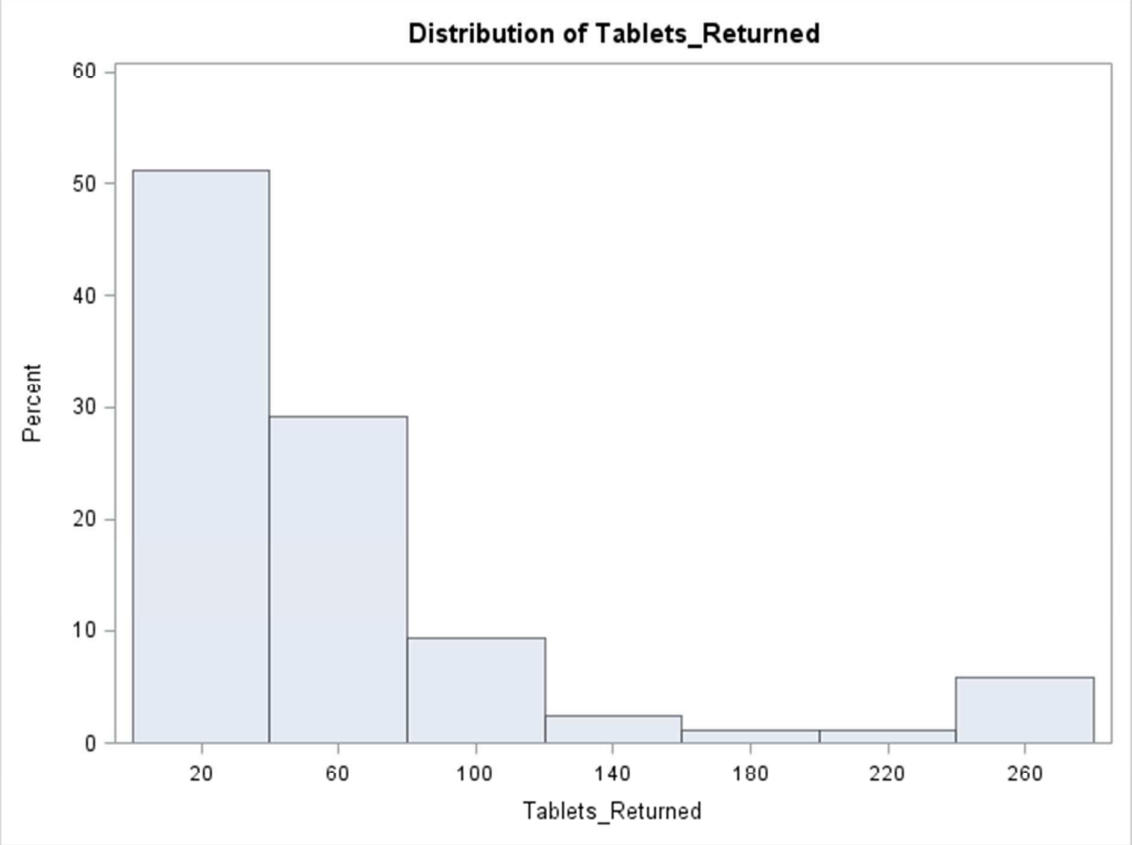

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Figure S- 5: Per protocol analysis of AusED driving simulator steering deviation in the final 30 minutes of a 90 minute afternoon drive (primary outcome)

Legend: This graph shows the steering deviation in cm for those participants who took study medication (either placebo or armodafinil) on the day of their three and six month study visits. Displayed p values are for the between group differences in change from baseline, at that visit.

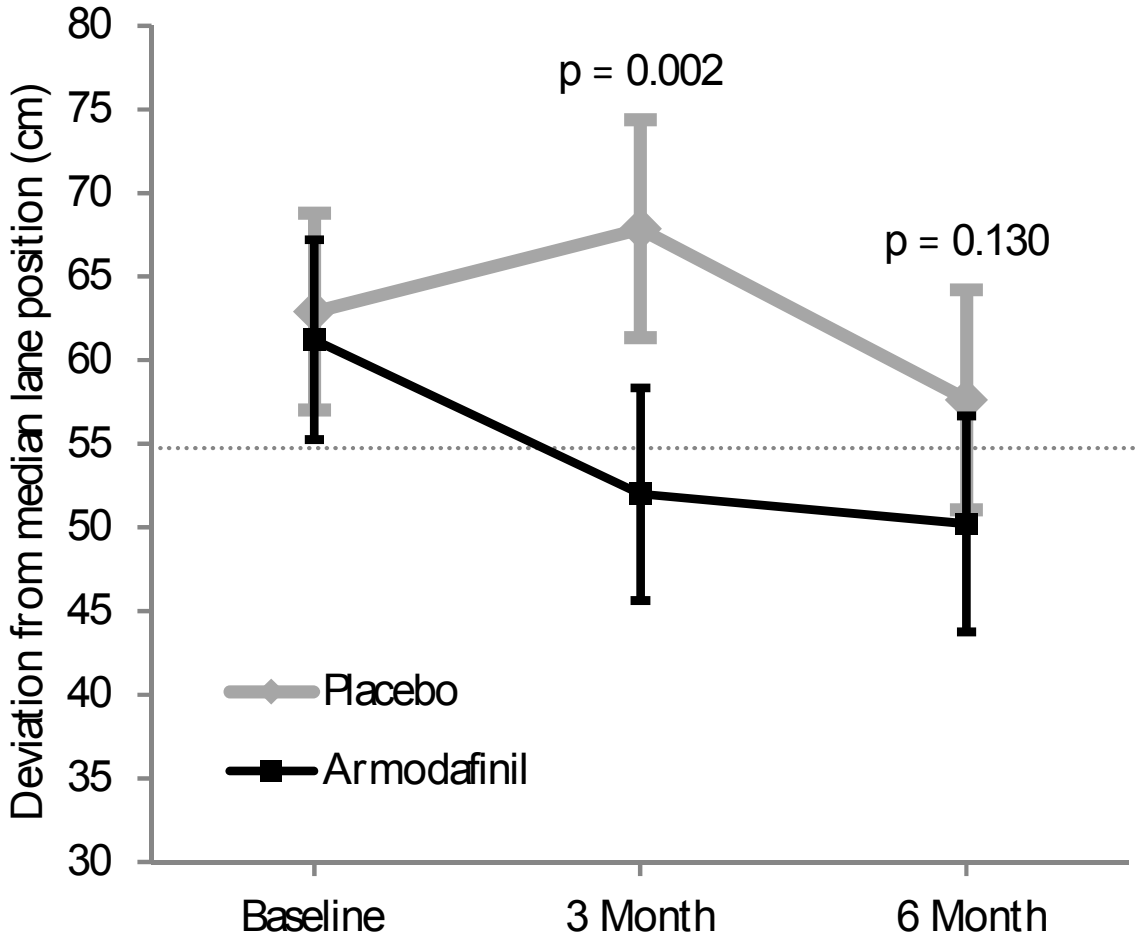

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Table S- 3: Primary, secondary and tertiary outcomes of drug study at 9 and 12 months.

Legend: Values for Baseline, 9 and 12 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.

		Placebo			Armodafinil			Net effect 9 months			Net effect 12 months		
		Baseline	9 months	12 months	Baseline	9 months	12 months		Effect size	p		Effect size	p
Primary outcome	AusED steering deviation (cm)	62.9 (3.1)	62.4 (3.1)	.	61.2 (3.1)	61 (3.2)	.	3.9(-5 to 12.9)	0.16	0.3882	.	.	.
Secondary outcomes	Total fat (g)	38647 (1347)	.	34614 (1393)*	39180 (1383)	.	34976 (1420)*	.	.	.	141(-1445 to 1727)	0.01	0.861
	Epworth score (/24)	10.2 (0.6)	8.8 (0.7)*	8.1 (0.6)*	9.3 (0.6)	7.8 (0.7)*	7.2 (0.6)*	0.4(-1 to 1.8)	0.09	0.584	0.2(-1.1 to 1.5)	0.05	0.764
	FOSQ total score (/120)	88 (1.9)	93.4 (2.2)*	94.9 (2.1)*	91.9 (2)	97.8 (2.2)*	99.2 (2.1)*	1.4(-3.6 to 6.4)	0.1	0.579	1.5(-3.3 to 6.3)	0.11	0.533
Tertiary outcomes	PVT reciprocal reaction time (1/ms)	3.94 (0.07)	3.95 (0.08)	.	3.83 (0.07)	3.81 (0.08)	.	0(-0.2 to 0.1)	-0.08	0.576	.	.	.
	n-back (% correct)	.	.	.	.	.	.	1.2(-3.6 to 5.9)	.	0.632	.	.	.
	Systolic blood pressure (mmHg)	124.8 (1.5)	124.4 (1.8)	124.7 (1.7)	129.6 (1.5)	126 (1.8)*	127.7 (1.7)	2.6(-1.4 to 6.7)	0.22	0.203	1(-2.7 to 4.7)	0.09	0.591
	Diastolic blood pressure (mmHg)	83.3 (1)	79.8 (1.3)*	80.8 (1.2)	85.2 (1.1)	80.4 (1.3)*	80.8 (1.2)*	0.5(-2.7 to 3.6)	0.06	0.778	1.1(-1.8 to 4)	0.14	0.449
	Framingham 10 year risk (%)	11 (1.1)	10.8 (1.2)	11.6 (1.2)	13.1 (1.1)	11.4 (1.2)*	11.6 (1.2)*	1.4(-0.2 to 3)	0.16	0.093	2.1(0.6 to 3.6)	0.25	**0.006**
	LDL Cholesterol (mmol/L)	3.2 (0.1)	3.1 (0.1)	3.2 (0.1)	3.1 (0.1)	2.9 (0.1)	2.8 (0.1)*	0.02(-0.19 to 0.22)	0.02	0.862	0.18(-0.02 to 0.37)	0.2	0.071
	HDL Cholesterol (mmol/L)	1.2 (0)	1.2 (0)	1.2 (0)	1.2 (0)	1.3 (0)*	1.2 (0)	0.06(-0.01 to 0.12)	0	0.093	-0.01(-0.07 to 0.05)	0	0.816
	Triglycerides (mmol/L)	1.9 (0.2)	1.7 (0.2)	1.9 (0.2)	1.8 (0.2)	1.4 (0.2)*	1.6 (0.2)	0.1(-0.3 to 0.5)	0.1	0.557	0.1(-0.2 to 0.5)	0.11	0.487
	HbA1c NGSP (%)	5.5 (0.2)	5.8 (0.4)	6 (0.5)	5.8 (0.2)	5.7 (0.4)	5.5 (0.3)	0.4(-0.9 to 1.7)	0.38	0.507	0.8(0 to 1.6)	0.71	0.056
	HOMA-IR (mmol/L)	5.5 (1)	6.7 (1.2)	5.1 (1.1)	7 (1)	5.8 (1.2)	6.7 (1.1)	2.6(0.2 to 5)	0.05	**0.035**	-0.3(-2.5 to 1.9)	-0.01	0.76
	Daily activity (count/24hours)	263952 (11664)	265248 (13968)	270864 (13824)	267840 (12240)	295200 (14256)*	291888 (13968)	21168(-8784 to 51120)	0.29	0.166	19728(-9504 to 48960)	0.27	0.185

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Figure S- 6: AusED driving simulator performance across the 90 minute drive at the 9 month visit.

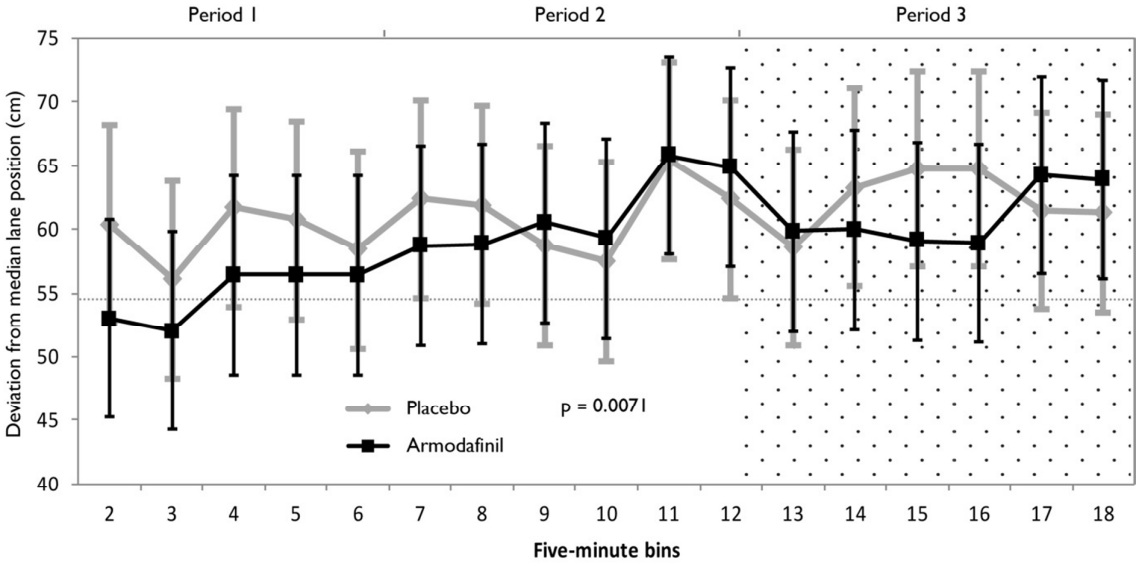

Figure S- 7: Dual-emission X-ray Absorptiometry (DXA) scan measured fat mass by drug allocation.

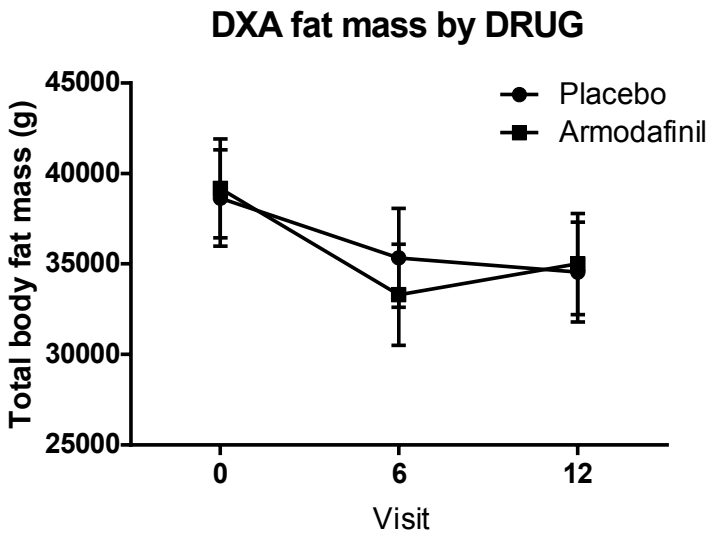

Figure S- 8: Dual-Emission X-Ray Absorptiometry (DXA) total fat mass by diet allocation
Legend: This graph shows the fat mass plotted at each timepoint for each of the diet groups and 95% confidence limits. INSERT: The difference between the groups in fat mass lost at 12 months (primary outcome) and the ±3300g MARGINS of equivalence (dotted vertical lines).

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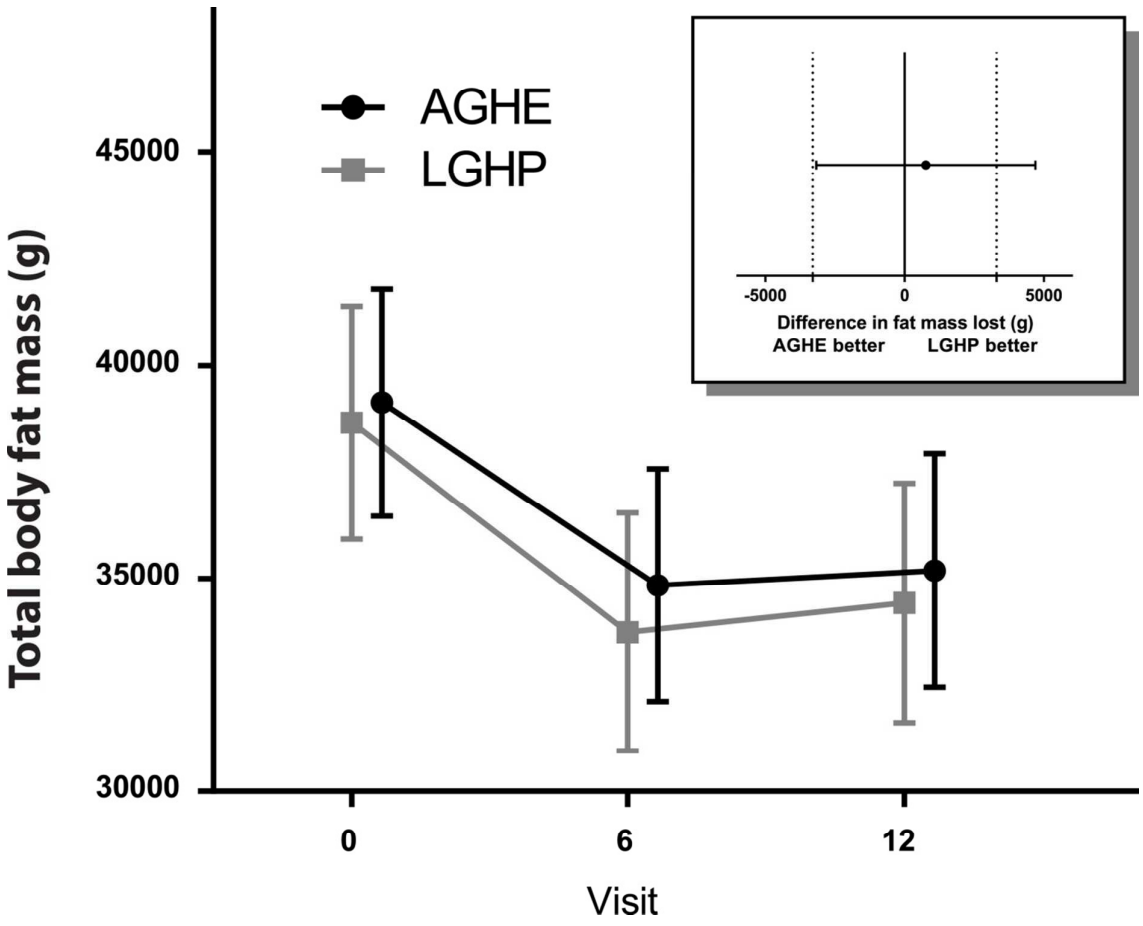

Figure S- 9: Weight by drug allocation at each major study visit

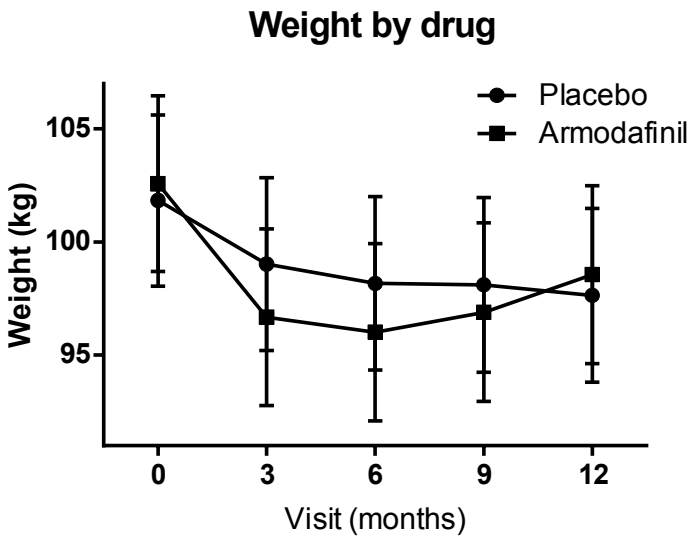

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Figure S- 10: Epworth Sleepiness Scale (ESS) scores
Legend: Placebo is represented by a grey line with diamond markers. Armodafinil is represented by a black line with square markers. Error bars represent 95% confidence intervals. There were no significant between group differences in improvements in Epworth Total Score.

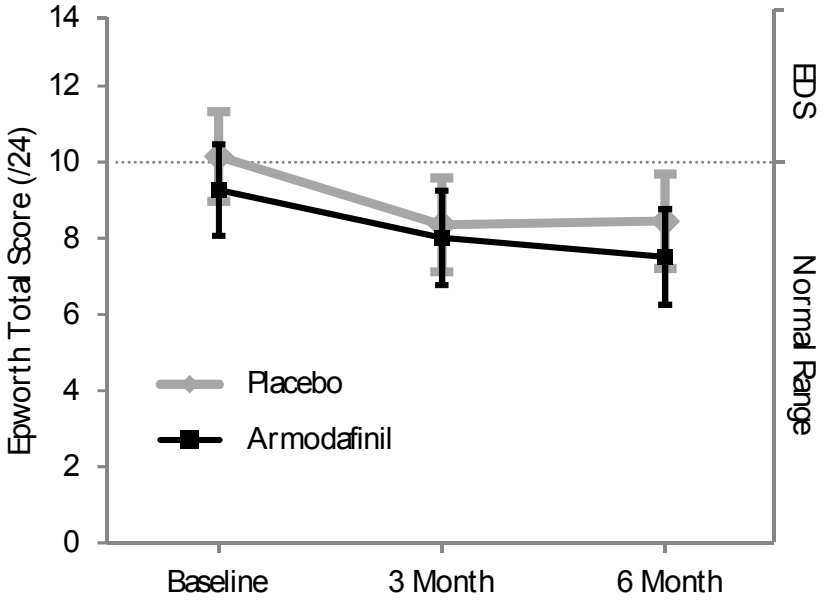

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Figure S- 11: Functional Outcomes of Sleep Questionnaire (FOSQ) scores.
Legend: Placebo is represented by a grey line with diamond markers. Armodafinil is represented by a black line with square markers. Error bars represent 95% confidence intervals. There were no significant between group differences at any timepoint,

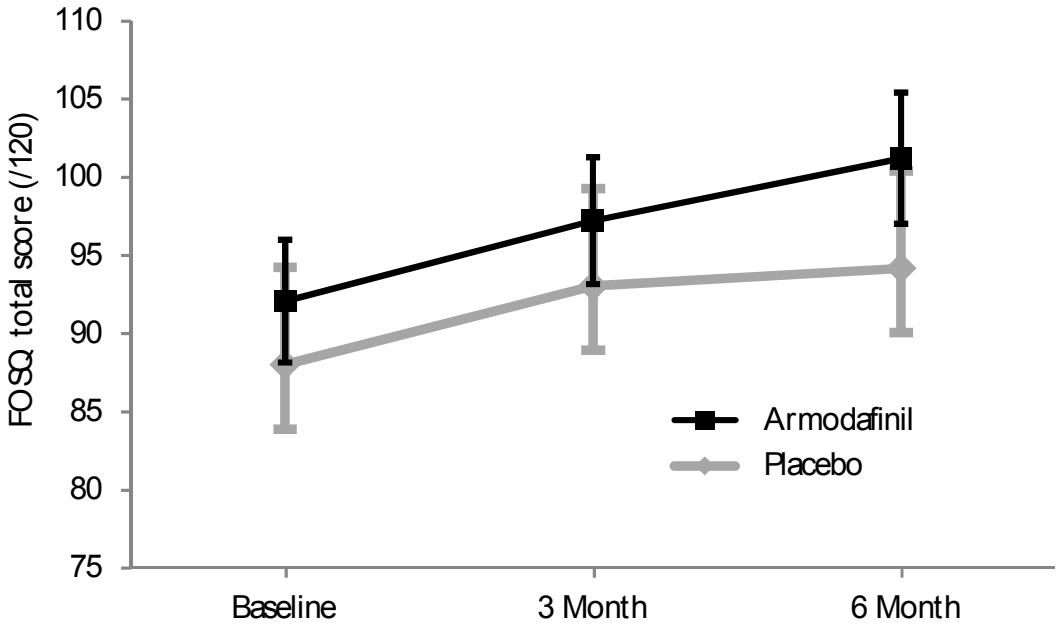

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Figure S- 12: Per protocol analysis of the change in Epworth Sleepiness Scale scores in quartiles of compliance
Legend: Higher values suggest improvement. Placebo is denoted by a grey line with diamonds indicating mean change from baseline. Armodafinil is denoted by a black line with squares indicating mean change from baseline. Error bars denote 95% confidence limits. Compliance quartiles are from 1 for the greatest number of tablets returned, suggesting lower medication use to 4 for the least number of tablets returned, suggesting higher medication use. There were no significant differences between the groups at any compliance quartile.

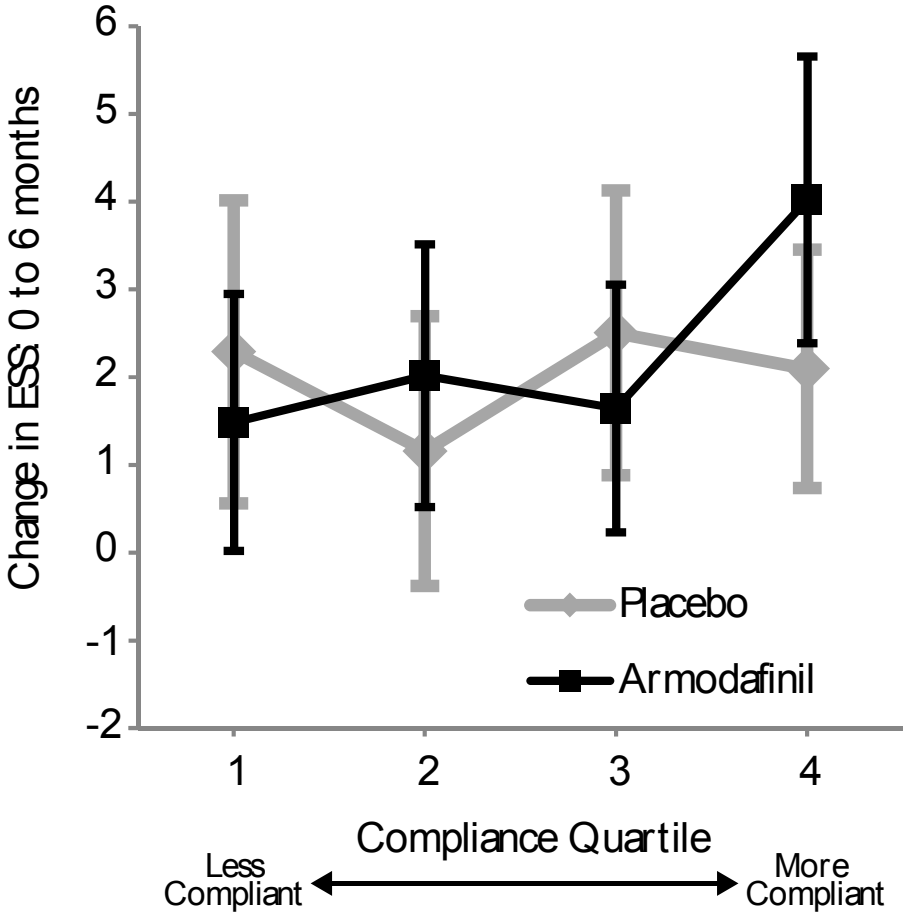

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Figure S- 13: Per protocol analysis of the change in Functional Outcomes of Sleep Questionnaire Scores in quartiles of compliance

Legend: Lower values suggest improvement. Placebo is denoted by a grey line with diamonds indicating mean change from baseline. Armodafinil is denoted by a black line with squares indicating mean change from baseline. Error bars denote 95% confidence limits. Compliance quartiles are from 1 for the greatest number of tablets returned, suggesting lower medication use to 4 for the least number of tablets returned, suggesting higher medication use. Displayed p value shows that those who were most compliant on armodafinil had greater improvement in FOSQ than those on placebo.

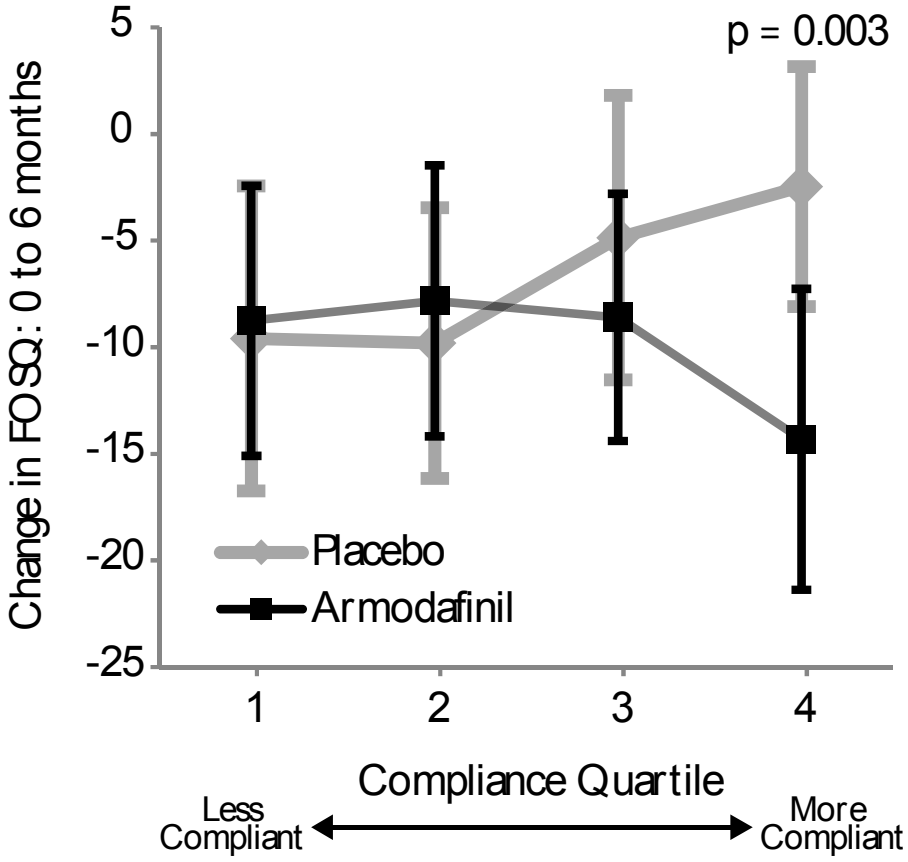

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Figure S- 14: Per protocol analysis of the AusED steering deviation at six months in quartiles of compliance
Legend: Compliance quartile was calculated based upon amount of study medication returned with quartile 1 the least compliant and 4 the most compliant group. There was no difference between placebo and armodafinil in improvement in driving simulator performance at any compliance quartile. There was a trend at the highest compliance (quartile 4) with 15.3cm greater improvement on armodafinil, 95%CI -1.6 to 32.2, p=0.075.

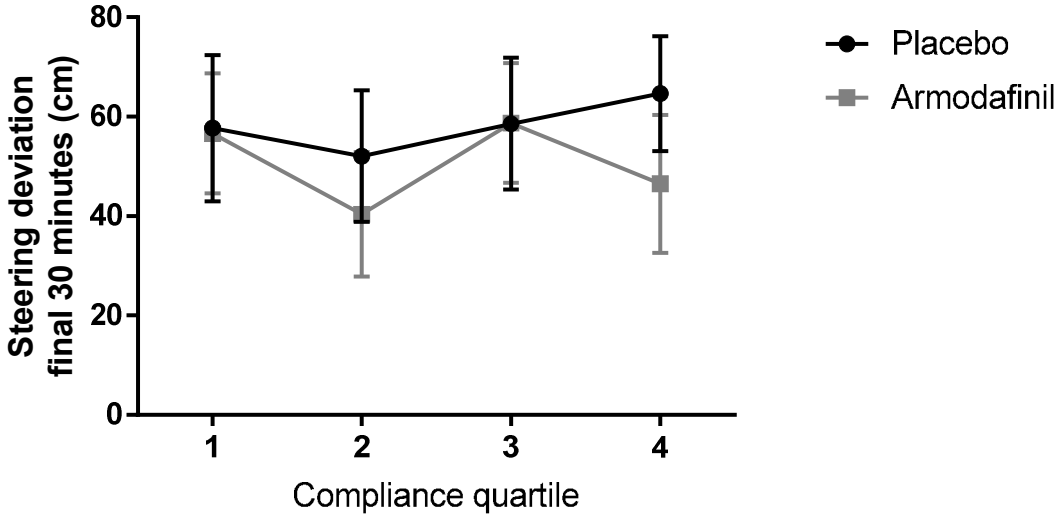

Figure S- 15: Daily activity count (raw activity counts) averaged per 24 hour period

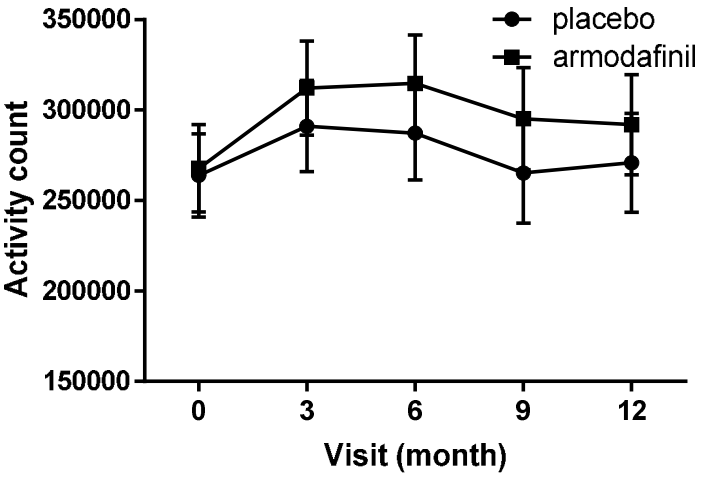

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Table S- 4: Other outcomes of the drug study

	Placebo					Armodafinil					Net effect 3 months	Effect size 3 months	p	Net effect 6 months	Effect size 6 months	p	Net effect 9 months	Effect size 9 months	p	Net effect 12 months	Effect size 12 months	p
	Baseline	3 months	6 months	9 months	12 months	Baseline	3 months	6 months	9 months	12 months												
Weight (kg)	101.8 (1.9)	99 (1.9)*	98.2 (1.9)*	98.2 (2)*	97.7 (2)*	102.6 (2)	96.7 (2)*	96 (2)*	96.9 (2)*	98.5 (2)*	3(1.1 to 4.9)	0.21	**0.002**	2.9(0.9 to 4.8)	0.2	**0.004**	2(0 to 4.1)	0.14	0.056	0(-2 to 2)	0	0.989
Apnea hypopnea index (/h)	43.1 (2.9)	.	38.7 (3.2)	.	35.3 (3.3)*	43.3 (3)	.	34.2 (3.2)*	.	38.2 (3.2)*	.	.	.	3.9(-1.4 to 9.2)	0.17	0.144	.	.	.	-3.1(-8.6 to 2.4)	-0.13	0.265
Total Sleep time (mins)	383.1 (7.4)	.	372.4 (8.6)	.	356.3 (9)*	377.5 (7.7)	.	378.4 (8.6)	.	387.1 (8.6)	.	.	.	6.2(-13.5 to 25.9)	0.13	0.534	.	.	.	29.6(9.3 to 50)	0.61	**0.005**
Arousal index (/h)	32.5 (2)	.	31.3 (2.3)	.	29.1 (2.4)	32.2 (2.1)	.	28.7 (2.3)	.	31.5 (2.3)	.	.	.	2(-2.3 to 6.4)	0.13	0.357	.	.	.	-3(-7.4 to 1.5)	-0.18	0.194
Glucose (mmol/L)	5.9 (0.2)	6 (0.2)	5.8 (0.2)	5.8 (0.2)	5.9 (0.2)	6.3 (0.2)	5.7 (0.2)*	5.9 (0.2)	5.7 (0.2)*	5.9 (0.2)	0.5(0.1 to 1)	0.29	**0.026**	0.1(-0.3 to 0.6)	0.08	0.544	0.3(-0.2 to 0.8)	0.18	0.226	0.2(-0.2 to 0.7)	0.13	0.336
Insulin (mU/L)	20.8 (2.5)	18.9 (2.7)	17.2 (2.6)	20.8 (2.8)	18.3 (2.7)	22.8 (2.5)	21.8 (2.6)	19.4 (2.6)	20.5 (2.9)	22.4 (2.7)	-2.1(-8.4 to 4.1)	-0.17	0.504	-0.6(-6.8 to 5.5)	-0.05	0.841	2.6(-4.4 to 9.5)	0.21	0.468	-2.5(-8.9 to 3.9)	-0.2	0.443
GGT (U/L)	35.1 (2.6)	33.1 (2.7)	33.7 (2.7)	33.1 (2.8)	31.2 (2.7)*	37.2 (2.7)	37.8 (2.7)	34.1 (2.8)	30 (2.9)*	31.3 (2.8)*	-3.3(-7.6 to 1.1)	-0.16	0.139	1.4(-3 to 5.8)	0.07	0.528	5(0.2 to 9.9)	0.25	**0.041**	1.5(-3.1 to 6)	0.07	0.533
ALT (U/L)	33.5 (2.2)	30.6 (2.5)	33.3 (2.5)	31.3 (2.7)	31.4 (2.6)	36.1 (2.3)	28.2 (2.4)*	24.8 (2.5)*	25.9 (2.7)*	27.3 (2.6)*	3.4(-2.3 to 9.2)	0.14	0.242	9.7(3.9 to 15.5)	0.41	**0.001**	6.9(0.4 to 13.5)	0.29	**0.038**	5.5(-0.6 to 11.7)	0.23	0.077
AST (U/L)	23.6 (1.2)	23.6 (1.4)	25 (1.4)	23.6 (1.6)	24.1 (1.5)	25.6 (1.3)	22.2 (1.4)*	20 (1.4)*	20.5 (1.6)*	20.8 (1.5)*	2.1(-1.3 to 5.4)	0.14	0.226	5.8(2.4 to 9.2)	0.4	**0.001**	3.9(0.1 to 7.8)	0.27	**0.046**	4.2(0.6 to 7.8)	0.3	**0.021**
SF36 physical composite score (/100)	62.4 (2.4)	67.5 (2.5)*	69.1 (2.5)*	66 (2.7)	70.2 (2.6)*	65.9 (2.4)	72.8 (2.5)*	69.7 (2.6)	72.2 (2.7)*	72.1 (2.6)*	2.9(-2.5 to 8.3)	0.16	0.294	-2.1(-7.5 to 3.4)	-0.11	0.458	4.5(-1.3 to 10.3)	0.25	0.131	-0.5(-6.1 to 5.1)	-0.03	0.863
SF36 mental composite score (/100)	73.7 (2.9)	73.9 (3.1)	74.9 (3.1)	75.8 (3.3)	80.4 (3.2)*	80.9 (2.9)	80.9 (3.1)	75.8 (3.2)	81.9 (3.3)	81.2 (3.2)	2.7(10.3 to -4.9)	0.13	0.485	-3.5(4.2 to -11.2)	-0.17	0.374	1.5(9.7 to -6.7)	0.07	0.72	-4.2(3.7 to -12.1)	-0.2	0.295
3FEQ emotional eating (/4)	2.2 (0.1)	2 (0.1)	2 (0.1)*	2 (0.1)*	2 (0.1)*	2 (0.1)	1.7 (0.1)*	1.9 (0.1)	1.9 (0.1)*	1.9 (0.1)	0.2(0 to 0.3)	0.22	0.055	-0.1(-0.2 to 0.1)	-0.08	0.47	0(-0.2 to 0.2)	0.03	0.817	0(-0.2 to 0.2)	-0.04	0.758
3FEQ cognitive restraint (/4)	2.4 (0.1)	2.8 (0.1)*	2.8 (0.1)*	2.8 (0.1)*	2.7 (0.1)*	2.3 (0.1)	2.9 (0.1)*	2.9 (0.1)*	2.9 (0.1)*	2.8 (0.1)*	0.2(0 to 0.4)	0.32	0.065	0.2(0 to 0.4)	0.4	**0.024**	0.1(-0.1 to 0.3)	0.25	0.185	0.1(-0.1 to 0.3)	0.23	0.206
3FEQ uncontrolled eating (/4)	2.3 (0.1)	2.1 (0.1)*	2.1 (0.1)*	2.1 (0.1)*	2 (0.1)*	2.3 (0.1)	1.9 (0.1)*	2 (0.1)*	2 (0.1)*	2 (0.1)*	0.1(-0.1 to 0.2)	0.12	0.403	0(-0.1 to 0.1)	0.01	0.945	0(-0.1 to 0.2)	0.07	0.635	0(-0.2 to 0.1)	-0.04	0.773

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Table S- 5: Primary and secondary outcomes of the diet trial

		AGHE					LGHP					Net effect 3 months	p	Net effect 6 months	p	Net effect 9 months	p	Net effect 12 months	p
		Baseline	3 months	6 months	9 months	12 months	Baseline	3 months	6 months	9 months	12 months								
Primary outcome	Total fat (g)	39136 (1349.3)	.	34838 (1386.3)*	.	35225 (1395.1)*	38664 (1385.6)	.	33747 (1418.2)*	.	34381 (1427.1)*	.	.	717(-848 to 2282)	0.367	.	.	577(-1037 to 2190)	0.482
Secondary outcomes	Apnea hypopnea index (/h)	41.9 (2.9)	.	38.9 (3.2)	.	37.4 (3.2)	44.5 (3)	.	33.9 (3.2)*	.	36.4 (3.3)*	.	.	7(2 to 13)	0.013	.	.	4(-2 to 10)	0.174
	Weight (kg)	103.9 (1.9)	99.1 (1.9)*	99 (1.9)*	99.4 (2)*	99.7 (1.9)*	100.5 (2)	96.4 (2)*	95.1 (2)*	95.6 (2)*	96.4 (2)*	-1(-3 to 1)	0.563	1(-1 to 3)	0.532	1(-1 to 3)	0.515	0(-2 to 2)	0.972
	Waist circumference (cm)	110.2 (1.4)	105.4 (1.5)*	105.8 (1.5)*	106 (1.5)*	106.7 (1.5)*	107.7 (1.4)	105.3 (1.5)*	102.8 (1.5)*	103.7 (1.5)*	104.7 (1.5)*	-2.3(-4.6 to 0.1)	0.06	0.7(-1.7 to 3.1)	0.585	0.2(-2.4 to 2.8)	0.879	-0.3(-2.8 to 2.2)	0.81
	IWQoL total score (/155)	58.1 (2.3)	47.6 (2.5)*	47.7 (2.5)*	48 (2.5)*	49 (2.5)*	56.4 (2.4)	49.2 (2.5)*	46.1 (2.5)*	46.5 (2.6)*	47.2 (2.5)*	-3.9(-8.3 to 0.5)	0.083	-0.3(-4.8 to 4.1)	0.89	-0.1(-4.9 to 4.7)	0.974	0.6(-3.9 to 5.2)	0.79

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Figure S- 16: Apnea hyponpnea index (AHI) by diet allocation (secondary outcome of diet study).

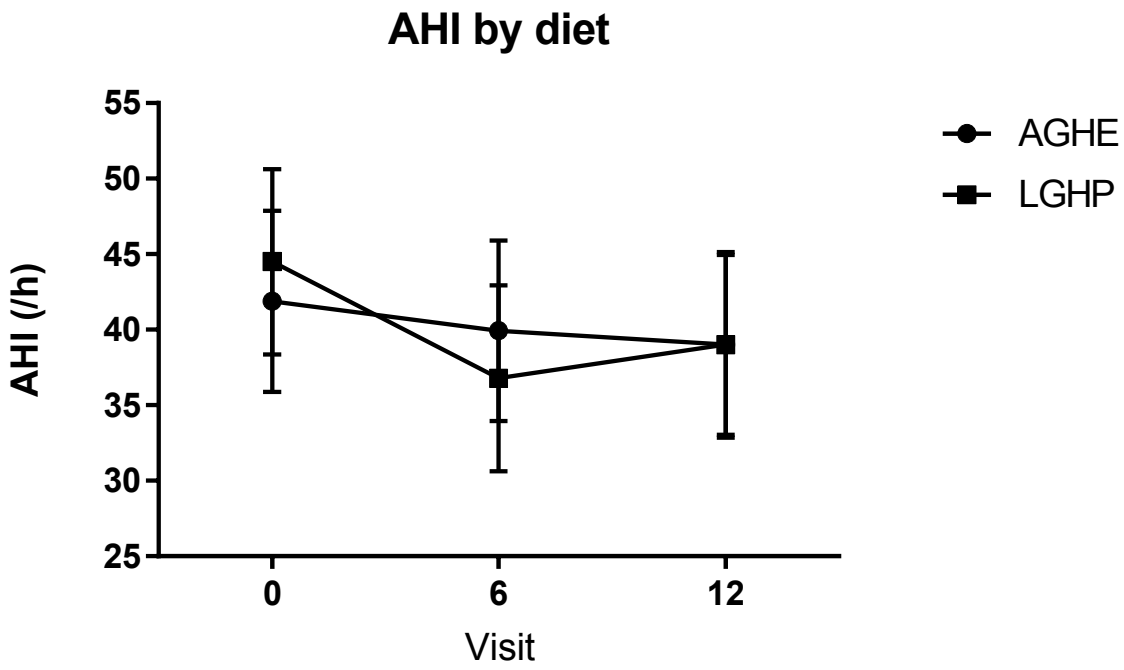

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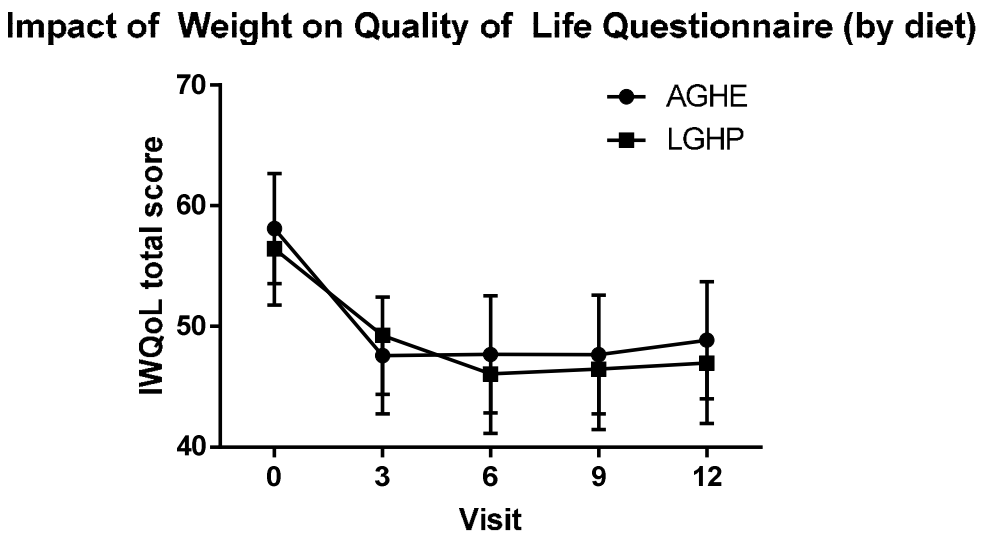
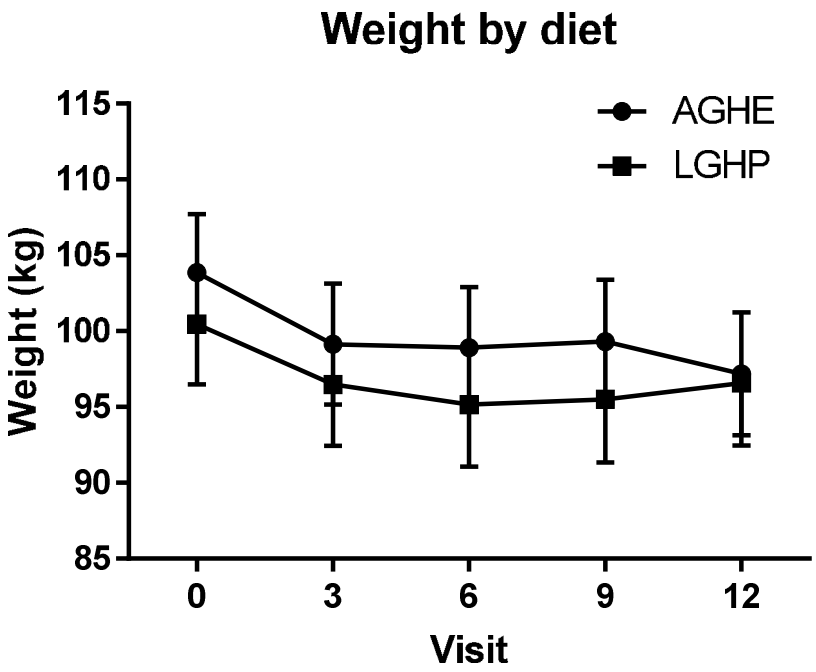
Figure S- 17: Impact of Weight on Quality of Life Questionnaire (secondary outcome of diet study



No significant differences between diet groups at any timepoint. Between baseline and 6 months the reduction was 10.4 (95%CI 8 to 12.8) and this was sustained to 12 months

Figure S- 18: Weight by diet allocation (secondary outcome of diet trial)



Weight loss was not significantly different between the groups. There was general weight loss of 5.2 kg (95%CI 3.6 to 6.7kg between baseline and 6 months, and this was sustained to 12 months

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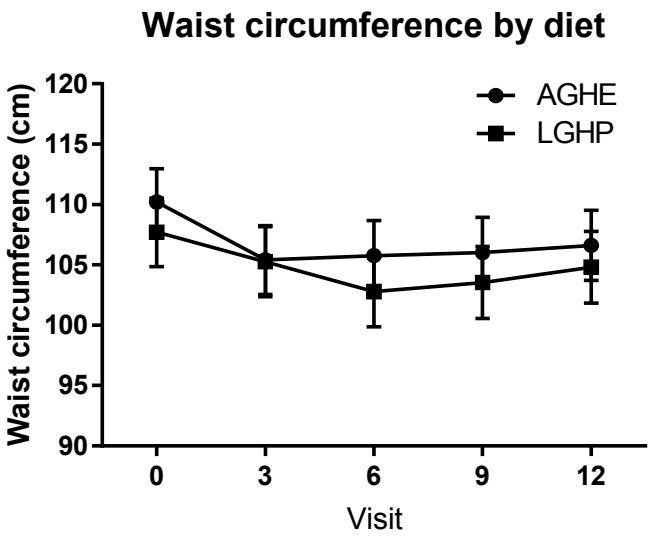
Figure S- 19: Waist circumference by diet allocation (secondary outcome of diet trial)



There were no significant differences between diet groups in terms of waist circumference changes.

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Figure S- 20: Fat mass loss correlated with change in apnea hypopnea index.
Legend: : This figure shows the change in fat mass and the change in AHI (baseline values minus the 12 month values) for all randomized patients regardless of drug of diet allocation.

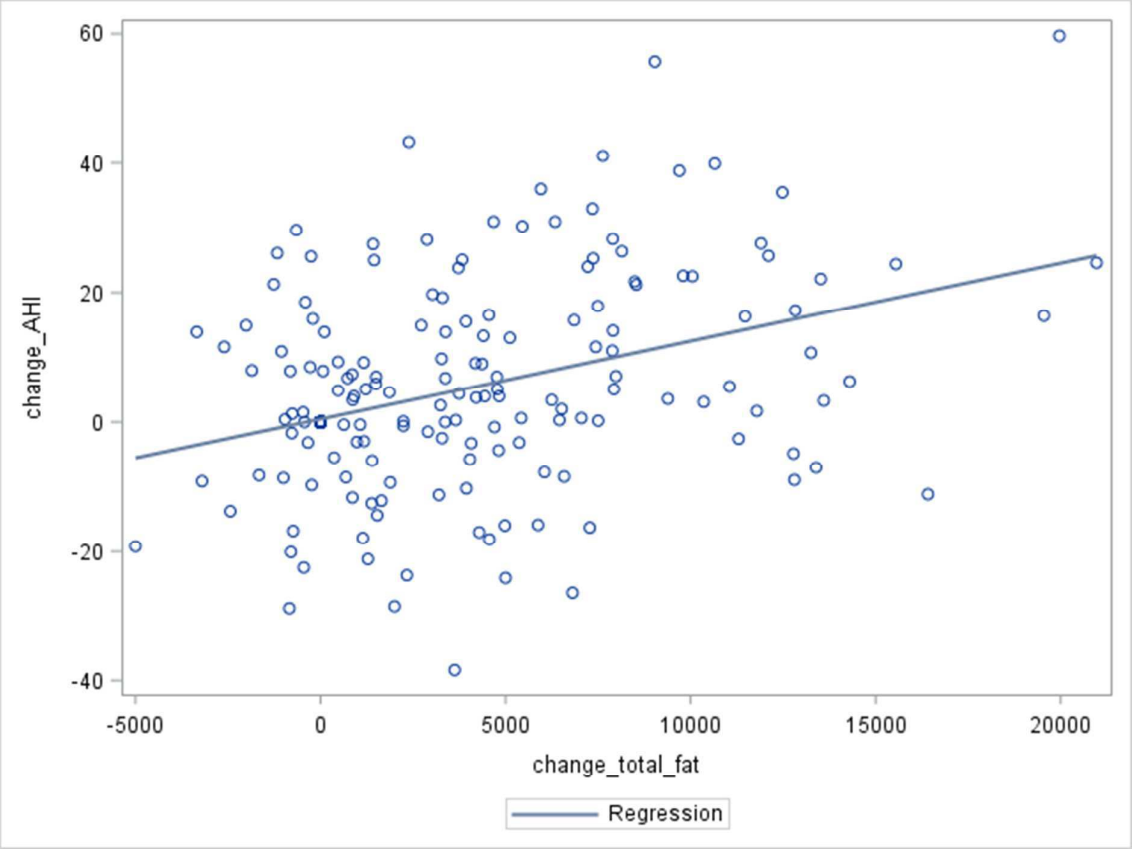

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Table S- 6: List of all adverse events reported during the study
Legend: MedDRA – Medical Dictionary for Regulatory Activities.

System Organ Class	MedDRA preferred term	Armodafinil	Placebo
Blood and lymphatic system disorders	Lymphadenopathy	1	0
Cardiac disorders	Palpitations	1	0
	Pericarditis	1	0
	Ventricular extrasystoles	1	0
Ear and labyrinth disorders	Ear pain	1	0
Eye disorders	Eye pruritus	1	0
	Visual impairment	1	0
	Retinal tear	0	1
Gastrointestinal disorders	Abdominal discomfort	1	0
	Abdominal pain	1	0
	Abdominal pain upper	1	0
	Constipation	3	2
	Defaecation urgency	0	1
	Diarrhoea	4	1
	Dry mouth	3	1
	Food poisoning	0	2
	Gastrooesophageal reflux disease	1	3
	Nausea	12	2
	Tongue movement disturbance	1	0
	Umbilical hernia, obstructive	1	0
	Vomiting	1	0
General disorders and administration site conditions	Asthenia	0	1
	Condition aggravated	5	1
	Energy increased	1	1
	Fatigue	3	1
	Feeling jittery	1	0
	Influenza like illness	7	2
	Pain	1	1
	Pyrexia	3	1
	Thirst	0	1
Immune system disorders	Seasonal allergy	0	1

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System Organ Class	MedDRA preferred term	Armodafinil	Placebo
Infections and infestations	Candida infection	1	0
	Cellulitis	1	0
	Bronchitis	0	1
	Gastroenteritis	1	1
	Gastroenteritis viral	2	0
	Gastrointestinal infection	1	0
	Influenza	2	5
	Lower respiratory tract infection	3	1
	Nasopharyngitis	4	7
	Pertussis	1	0
	Pneumonia	1	0
	Respiratory tract infection	1	0
	Sepsis	1	0
	Pharyngitis	0	2
	Rash pustular	0	1
	Sinusitis	3	2
	Skin infection	0	1
	Tonsillitis	1	1
	Urinary tract infection	0	1
	Viral upper respiratory tract in	0	1
Injury, poisoning and procedural complications	Arthropod bite	1	1
	Contusion	0	1
	Epicondylitis	0	1
	Fall	1	0
	Foot fracture	1	0
	Joint injury	1	0
	Ligament sprain	1	0
	Meniscus injury	1	0
	Muscle rupture	1	0
	Tooth injury	1	0
	Mountain sickness acute	0	1
	Muscle strain	0	1
	Procedural vomiting	0	1
	Tibia fracture	0	1
Metabolism and nutrition disorders	Haemoglobin decreased	0	1
	Type 2 diabetes mellitus	1	0
	Vitamin D deficiency	1	0

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System Organ Class	MedDRA preferred term	Armodafinil	Placebo
Musculoskeletal and connective tissue disorders	Arthralgia	4	1
	Back pain	2	2
	Bursitis	1	0
	Gouty tophus	1	0
	Limb discomfort	0	1
	Muscle spasms	1	1
	Musculoskeletal stiffness	1	0
	Osteoarthritis	2	0
	Pain in extremity	3	2
	Plantar fasciitis	0	2
	Temporomandibular joint syndrome	2	0
	Trismus	2	0
Nervous system disorders	Advanced sleep phase	0	1
	Carpal tunnel syndrome	1	0
	Disturbance in attention	0	1
	Dizziness	11	2
	Dizziness postural	1	1
	Dyskinesia	1	0
	Headache	15	5
	Irregular sleep phase	1	0
	Lethargy	2	2
	Memory impairment	0	1
	Migraine	3	3
	Migraine with aura	0	1
	Paraesthesia	3	0
	Poor quality sleep	0	1
	Presyncope	1	0
	Sinus headache	1	0
Psychiatric disorders	Abnormal dreams	1	0
	Aggression	2	0
	Agitation	0	2
	Anxiety	4	1
	Depressed mood	0	1
	Apathy	1	0
	Initial insomnia	3	5
	Insomnia	6	2
	Irritability	2	1
	Libido decreased	0	2
	Middle insomnia	0	1
	Panic attack	0	0
	Paranoia	0	0
	Soliloquy	1	0

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System Organ Class	MedDRA preferred term	Armodafinil	Placebo
Renal and urinary disorders	Chromaturia	1	0
	Micturition urgency	0	1
	Nocturia	1	0
	Pollakiuria	1	1
	Renal impairment	1	0
Reproductive system and breast disorders	Endometriosis	1	0
Respiratory, thoracic and mediastinal disorders	Asthma	1	0
	Cough	5	3
	Dyspnoea	1	0
	Haemoptysis	1	0
	Nasal congestion	0	1
	Oropharyngeal pain	1	5
	Respiratory tract congestion	0	1
Skin and subcutaneous tissue disorders	Dry skin	0	1
	Hirsutism	0	1
	Hyperhidrosis	1	0
	Night sweats	0	1
	Psoriasis	1	1
	Rash	1	2
Surgical and medical procedures	Transient acantholytic dermatosis	0	1
	Bariatric gastric balloon insert	0	1
	Drug rehabilitation	0	1
	Gastric banding reversal	0	1
	Urethral stent insertion	1	0
Vascular disorders	Hypotension	1	0
	Hypertension	0	1

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Figure S- 21: Systolic blood pressure by drug allocation (tertiary outcome of drug study)

Legend: Placebo is represented by a grey line with diamond markers. Armodafinil is represented by a black line with square markers. Error bars represent 95% confidence intervals. Displayed p value denotes the difference between the groups at that timepoint

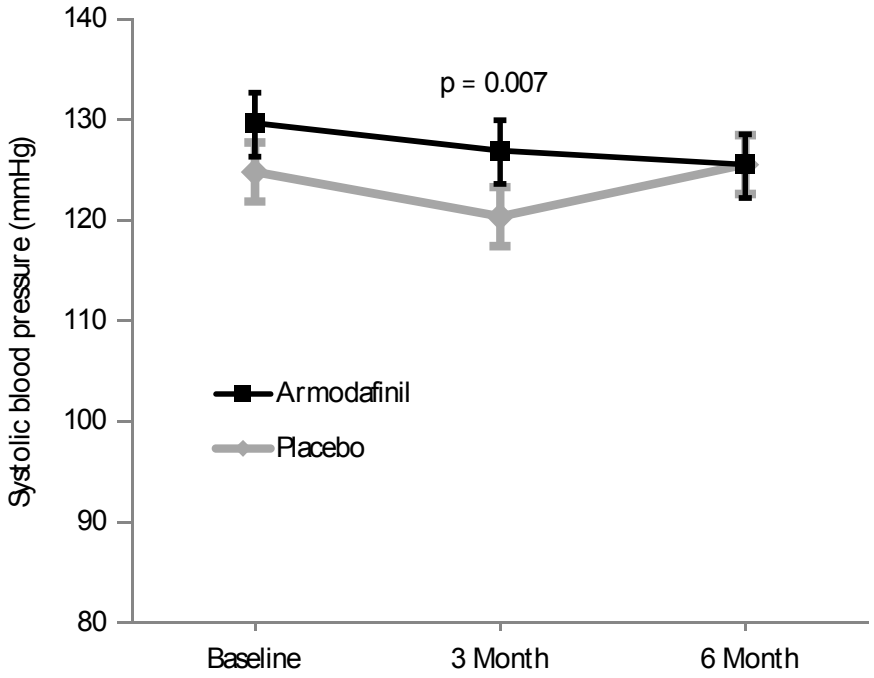

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Figure S- 22: Diastolic blood pressure by drug allocation (tertiary outcome of drug study)
Legend: Placebo is represented by a grey line with diamond markers. Armodafinil is represented by a black line with square markers. Error bars represent 95% confidence intervals. There were no significant between group differences at any timepoint,

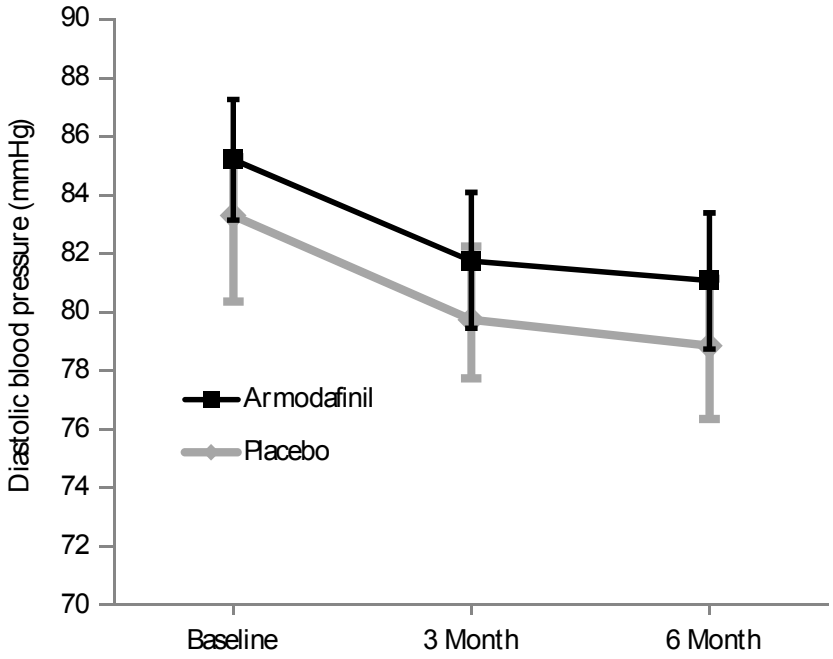

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Figure S- 23: Systolic blood pressure in patients who had no weight change
Legend: This figure shows the blood pressure at each timepoint for just those patients who had no significant weight change at 6 months (i.e. 6 month weight ± 2kg of baseline weight). Placebo is represented by a grey line with diamond markers. Armodafinil is represented by a black line with square markers. Error bars represent 95% confidence intervals. Displayed p value denotes the difference between the groups at that timepoint

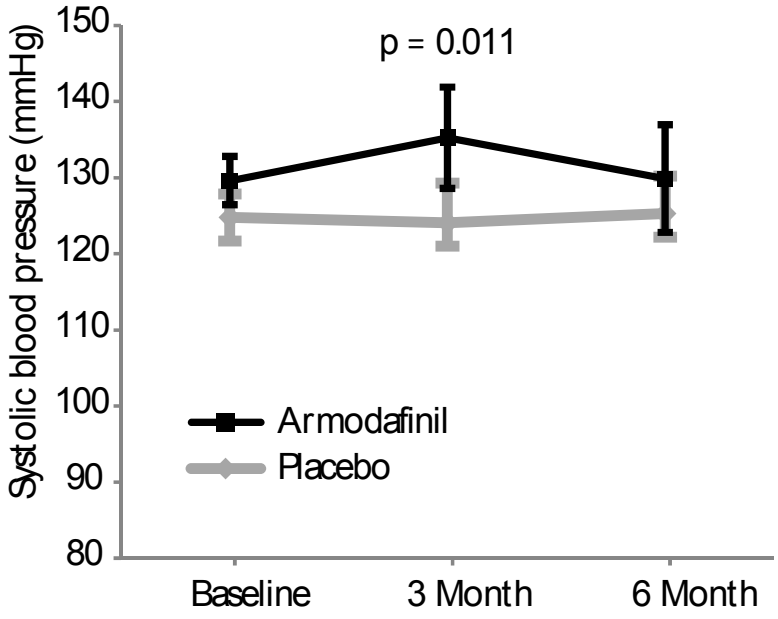
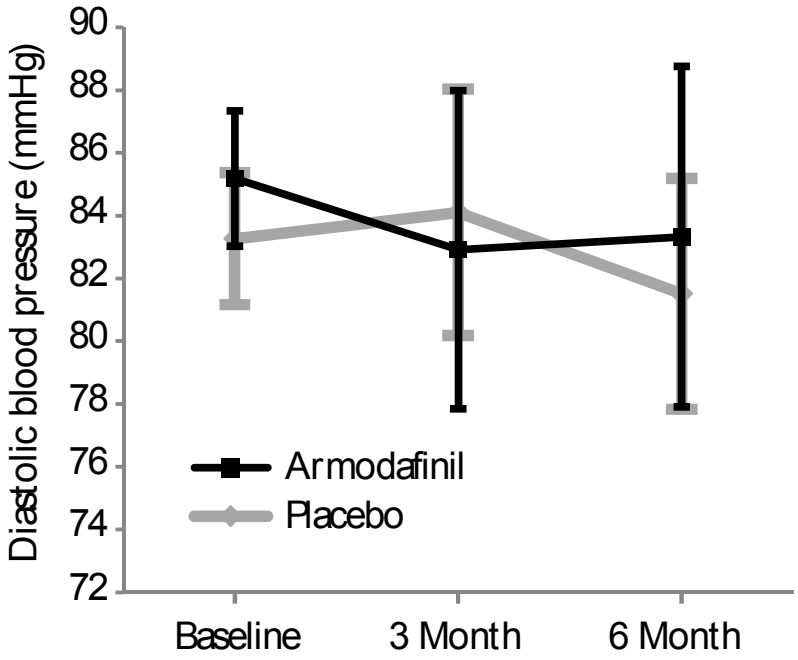


Figure S- 24: Diastolic blood pressure in patients who had no weight change
Legend: This figure shows the blood pressure at each timepoint for just those patients who had no significant weight change at 6 months (i.e. 6 month weight ± 2kg of baseline weight). Placebo is represented by a grey line with diamond markers. Armodafinil is represented by a black line with square markers. Error bars represent 95% confidence intervals. There were no significant between-group differences at any timepoint.



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