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CPAP Treatment of Sleepy Patients with Milder OSA:

Results of the CATNAP Randomized Clinical Trial

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required data analysis for the DSMB prior to unblinding; Bethany Staley was responsible for study design and data collection and interpretation; Dr. J. Richard Landis contributed to study design and served for a period of time as Executive Secretary of the Data Safety Monitoring Board; Drs. Ferguson, George, Schulman, Greenberg, Rapoport, Walsleben, and Lee-Chiong contributed to study design, supervised data collection, interpreted the data, and edited and reviewed the manuscript; Dr. Samuel Kuna was responsible for study design, data collection, interpretation of the data, and writing of the manuscript.

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At A Glance Commentary:

Scientific Knowledge on the Subject

One in five adult males suffer from mild to moderate obstructive sleep apnea (OSA), 28% of whom experience excessive daytime sleepiness. Continuous Positive Airway Pressure (CPAP) is the primary treatment for OSA, but this efficacy has been primarily

demonstrated in those with more severe disease. It remains unclear whether CPAP is effective in the largest segment of the OSA population, particularly with respect to daily functioning and daytime sleepiness. The few randomized controlled trials (RCT) of CPAP efficacy in patients with milder OSA have produced conflicting results; principally because of methodological limitations.

What This Study Adds to the Field

Sleepy patients with mild and moderately severe OSA had greater functional improvement after 8 weeks of CPAP therapy compared to sham CPAP. Compared to placebo, CPAP treatment also produced clinically meaningful changes in mood and self-reported daytime sleepiness. As a multisite study conducted at large and smaller clinical practice sites, our results are highly generalizable and indicate the efficacy of this therapy in treating sleepy patients with less severe OSA.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

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Abstract

Rationale: Twenty-eight percent of people with mild to moderate obstructive sleep apnea experience daytime's sleepiness, which interferes with daily functioning. But, it remains unclear whether treatment with continuous positive airway pressure improves daytime function in these patients.

Objectives: To evaluate the efficacy of continuous positive airway pressure treatment to improve functional status in sleepy patients with mild and moderate obstructive sleep apnea.

Methods: Patients with self-reported daytime sleepiness (Epworth Sleepiness Scale score > 10) and an apnea-hypopnea index with 3% desaturation ≥ 5 and < 30 events/hr were randomized to 8 weeks of active or sham continuous positive airway pressure treatment. Following the 8-week intervention, participants in the sham arm received 8 weeks of active continuous positive airway pressure treatment.

Measurements and Main Results: The Total score on the Functional Outcomes of Sleep Questionnaire was the primary outcome measure. The adjusted mean change in the Total score following the first eight-week intervention was 0.89 for the active group (n=113) and -0.06 for the placebo group (n=110) (p = 0.006). The group difference in mean change corresponded to an effect size of 0.41 (95% CI from 0.14 to 0.67). The mean (SD) improvement in FOSQ Total score from the beginning to the end of the cross-over phase (n=91) was 1.73 ± 2.50 (t(90)=6.59, p<0.00001) with an effect size of 0.69.

Conclusions: Continuous positive airway pressure treatment improves the functional outcome of sleepy patients with mild and moderate obstructive sleep apnea.

Abstract word count: 239

Key Words: CPAP, obstructive sleep apnea, daytime sleepiness, randomized clinical trial, functional status

Obstructive sleep apnea (OSA) is characterized by episodic collapse of the pharyngeal airway during sleep causing intermittent hypoxemia and fragmented sleep. OSA is common; up to 28% of females and 26% of males have five or more apneas and hypopneas per hour of sleep (AHI) with 28% of this population reporting excessive daytime sleepiness (1, 2) Based on the AHI, disease severity is categorized as mild (5 ≥ AHI < 15 events/hr), moderate (15 ≥ AHI < 30 events/hr), and severe (AHI ≥ 30 events/hr).(3) OSA is associated with premature death, hypertension, ischemic heart disease, stroke, insulin resistance, and work- and driving-related accidents.(4-7)

Continuous positive airway pressure (CPAP) is the primary treatment for OSA. CPAP prevents pharyngeal airway collapse during sleep thereby improving the quality of sleep and oxygen saturation.(8) CPAP is reported to improve daytime sleepiness and other daytime impairments, reduce cardiovascular risk, improve insulin sensitivity, increase neurobehavioral performance, and enhance quality of life.(9-11) However this evidence is based mostly in studies of patients with severe OSA.(12) It remains unclear whether CPAP is effective in those with milder disease, particularly with respect to daily functioning and daytime sleepiness. The few randomized controlled trials (RCT) of CPAP efficacy in patients with milder OSA have produced conflicting results; principally because of methodological limitations.(9) The purpose of the CPAP Apnea Trial North American Program (CATNAP) was to determine the efficacy of CPAP treatment for functional improvement in sleepy patients with mild and moderate OSA. In this double-blind, randomized, placebo-controlled, parallel-groups study, we hypothesized that the mean change in functional status following eight weeks of treatment would be greater in participants receiving active CPAP compared to sham CPAP, the placebo intervention.

We also hypothesized an improvement in the change in secondary outcomes – mean self-reported sleepiness, objectively measured sleepiness, mood, and mean arterial blood pressure – at 8 weeks post-treatment in those individuals treated with active CPAP compared to sham CPAP.

METHODS

Sample

Participants were recruited from consecutive patients. Eligibility criteria included patients with newly diagnosed milder OSA (5≤ AHI <30 events/hr) who were naïve to CPAP and had an Epworth Sleepiness Scale (ESS) score >10.(13) Additionally, participants had a stable medical condition in the past 3 months, greater than 5th grade reading level, and no history of other sleep disorder, current pregnancy, substance abuse, sleepiness-related driving accident or sleepiness-sensitive occupation. The study was approved by the Institutional Review Board at each participating site and informed consent was obtained from all participants.

The primary endpoint was the change after 8 weeks of treatment in Functional Outcomes of Sleep Questionnaire (FOSQ) Total score (see Online Supplement).(14) Secondary analyses included the FOSQ subscale scores, generic functional status (SF-36),(15) self-reported sleepiness (ESS score),(13) objective sleepiness (lapses in attention measured by the Psychomotor Vigilance Task [PVT]),(16) mood (Total Mood Disturbance scale on the Profile of Mood States [POMS]),(17) and mean 48 hour ambulatory blood pressure (see Online Supplement).

Procedures

Diagnostic and CPAP titration polysomnograms were performed according to standard procedures (see Online Supplement).(18) Following a diagnostic polysomnogram and completion of the baseline assessment, participants were randomized to 8 weeks of either active or sham CPAP (see Online Supplement)(19) and performed a manual CPAP titration polysomnogram or sham CPAP polysomnogram.(19) The sham CPAP looked identical to active CPAP, but delivered <1.0 cm H2O of pressure.(19) All polysomnograms were scored at a centralized reading laboratory that selected the optimal setting for active treatment. An unblinded polysomnographic technologist performed the CPAP set-ups (Philips Respironics, Monroeville, PA) and distributed CPAP data cards (Philips Respironics Encore SmartCard™). Participants sent these cards weekly to the clinical center.

Participants completed the assessment battery at baseline and 8-weeks of intervention. In addition, they completed the FOSQ weekly at home and recorded on the CPAP unit's data card. When the 8-week intervention was completed, participants were informed of their assigned intervention. Those assigned to active treatment were dismissed from the study; those assigned to sham CPAP were crossed over to the active CPAP treatment protocol.

Statistical Analysis

Sample size was designed to achieve at least 80% power, using n=123 per group with an effect size of at least 0.36.(9) The primary comparison was a modified intent-to-treat (ITT) analysis of participants initiated on the assigned intervention and having a follow-up FOSQ score. The between-group hypotheses for all endpoints were tested using an Analysis of Covariance (ANCOVA) model controlling for baseline value, clinical center,

and statistically different clinical and demographic characteristics (Table 1). Last Observation Carried Forward (LOCF) imputation was specified for participants missing Week 8 results (weekly FOSQ Total Scores displayed in Online Supplement Table E1). Statistical significance ($p < 0{\cdot}05$) of improvements was assessed using paired *t* tests.

Baseline values for the cross-over phase of the study were defined as the results obtained at the completion of the sham CPAP intervention. Paired t-tests were performed on results from baseline and end of the 8-week, active intervention.

The study was registered with ClinicalTrials.gov, number NCT00127348.

RESULTS

Data collection commenced in 2003 and ended in 2008. Of the 385 participants screened and consented, 281 were randomized (Figure 1). Of these, 42 withdrew following randomization but before exposure to active or sham CPAP (active treatment n = 20) primarily due to time constraints or desiring immediate treatment. These participants were excluded from all analyses. Of the 239 randomized and exposed participants, mean age was 49.5 ± 10.9 yr in the active CPAP group (n = 121) and 51.7 ± 11.9 yr in the sham CPAP group (n = 118), with 55% and 63% males, and 79.3% and 76.3% Caucasians respectively (Table 1). The mean ESS score was 15.2 ± 3.4 and 14.7 ± 3.1 for active and placebo treatment, respectively. Among the 239 randomized and exposed participants, 17 were missing baseline or final FOSQ Total score after applying LOCF, leaving 223 participants in the modified ITT cohort (113 active CPAP, 110 sham CPAP). The only differences at baseline between the two groups were difference in the SF 36 Mental Component and POMS Total Mood Disturbance scores. (Table 1). It is unclear why there were differences in mood between the two

randomized groups. However, these differences were not clinically meaningful (effect size (ES) of -0.29). Regarding lifetime and current medical conditions, the two groups differed with regard to having the lifetime diagnosis of syncope, but there were no statistically significant differences for current conditions (Tables E3a, E3b Online Supplement). Concomitant medications for both groups are listed in Table E4 of the Online Supplement.

The mean AHI (with >3% desaturation) on diagnostic PSG in participants in the active and sham CPAP arms was 12.8 ± 6.4 and 12.5 ± 6.5 events/hr respectively (p = 0.69). Sixty-two percent (75/121) of participants in the active arm and 64% (75/118) of participants in the sham CPAP arm had mild sleep apnea (5 ≤ AHI < 15 w/3% desaturation) on baseline testing. On the PSG performed with sham CPAP in those participants randomized to that intervention, the mean AHI (with >3% desaturation) was 14.6 ± 12.3 events/hr and was significantly different from the AHI (with >3% desaturation) on the diagnostic study (p = 0.03), but the 2.4 event/hr difference was not clinically meaningful (effect size of 0.22). As expected, there was a statistically significant difference between the change with titration in the active CPAP group compared to the sham group (-11.9, -2.4, p = 0.000, ES = -1.61).The active CPAP setting in participants randomized initially to active treatment was 8.1+/-2.2 (range 4 – 14) cm H_2O. On the CPAP titration PSG performed in participants randomized to active CPAP, the mean AHI with >3% desaturation at the pressure setting selected for subsequent treatment was 0.9 ± 1.3 events/hr and was significantly less than that on the diagnostic study (p<0.0001).

Primary Efficacy Analyses

The mean ± SD FOSQ Total score at baseline in the primary efficacy cohort was 13.91 ± 3.02 and 14.43 ± 2.78 in the active and sham CPAP groups, respectively (p = 0.18) (Figure 3 and Table 2). The unadjusted mean change in FOSQ Total score from baseline to Week 8 in the modified ITT sample was 0.98 ± 2.89 for the active CPAP group and -0.14 ± 2.61 for the placebo group. Based on the primary (site-weighted and baseline-adjusted) ANCOVA model, the group difference in mean changes in FOSQ Total score from baseline to Week 8 was 0.95 (SE 0.34, p = 0.006, 95% CI 0.27 to 1.62)(Table 3). The group difference in mean change corresponded to an effect size of 0.41 (95% CI 0.14 to 0.67).

In descriptive sensitivity analyses, the magnitude of group differences in changes from baseline FOSQ Total score in the modified ITT analysis cohorts was also compared: (1) after disabling the LOCF imputation and (2) in Per Protocol cohorts requiring a mean CPAP use ≥ 4 hr/day (Table 4). These analyses suggested that our primary results may have been conservatively estimated. Seventeen participants required LOCF imputation in order to be included in the modified ITT analyses. Disabling the LOCF imputation resulted in a more than a 25% increase in the median percentage improvement in the FOSQ Total score in the active CPAP group, from 5.8% to 7.3%, but had little effect on the median change in the sham CPAP group. Overall, disabling LOCF increased the (unadjusted) effect size from 0.41 to 0.48 (95% CI 0.21 to 0.76). In the Per Protocol cohort of active treatment participants with an average daily CPAP use of at least 4 hours, the median percentage change in FOSQ Total score increased another 56%, from 7.3% to 11.4%. The median Per Protocol change in the

sham CPAP group was -1.2% to 1.9%. There was little change in the effect size for this cohort (ES = 0.49, 95% CI 0.07 to 0.90).

Secondary Efficacy Analyses

The adjusted mean differences between groups showed significant improvements in all FOSQ subscale scores except Social Outcome, and Intimacy and Sexual Relationships (Table 3). The adjusted mean changes from baseline to Week 8 for the other secondary outcome measures are in Table E6 and E7 in the Online Supplement. Significant improvements in the active CPAP group compared to the sham CPAP group occurred in the following SF-36 subscales: Physical Component, Physical Functioning, Bodily Pain, General Health and Vitality (*p* values < 0.04). The unadjusted mean change in the ESS score was -2.6 ± 4.3 for the active group (p < 0.00001) and -0.5 ± 3.5 in the sham group (p = 0.12). The adjusted mean difference between groups was -1.8 (SE 0.5) (*p* = 0.001; 95% CI bounds -2.8 to -0.8). Total Mood Disturbance on the POMS and the subscales of Fatigue, Confusion-Bewilderment, and Vigor were significantly improved in the active versus sham CPAP group (p values ≤ 0·014). No significant difference was observed in the change of the number of lapses on PVT between the two groups (*p* = 0.12).

The 48-hour ambulatory blood pressure recordings were analyzed for mean adjusted change in daytime pressure, nocturnal pressure, and nocturnal dipping of the systolic, diastolic, and mean arterial pressures as well as heart rate. The study was not powered for these secondary outcomes and, due to technical difficulties, results for the modified ITT analysis were obtained in only about half of the participants in each group.

The sole significant difference in blood pressure between the two groups was the mean adjusted change in daytime diastolic blood pressure.(p = 0.048).

CPAP Use

The mean ± SD duration of CPAP use was 4.0 ± 2.0 and 3.1 ± 2.1 hr/day in the active CPAP and sham CPAP groups, respectively [$t(313) = 3{\cdot}3$, $p = 0.001$]. We conducted Pearson correlations to determine the strength of the linear association between mean daily hours of CPAP use and change in FOSQ Total score. The correlation in the active treatment group was moderately large and statistically significant ($r = 0.25$, $p = 0.008$, $n = 101$). In contrast, the correlation in the sham CPAP group was small and not statistically significant ($r = 0.15$, $p = 0.12$, $n = 97$). Thus, 6.4% of the variance in FOSQ Total score improvements could be explained by a linear association with mean CPAP use in the active treatment group. In contrast, only 2.3% of FOSQ Total score improvement variance was explained in the sham CPAP group, and the association did not achieve statistical significance.

Cross-over Cohort Analyses

Of the 118 subjects randomized and exposed to sham CPAP, 102 (86.4%) were enrolled into the 8-week active CPAP intervention. Of these 99 had a FOSQ Total score at the end of their sham CPAP intervention, i.e. the baseline measurement used in the cross over analysis. Their demographic characteristics are reported in Table E8 of the Online Supplement. The mean (SD) improvement in FOSQ Total score from the beginning to the end of the cross-over phase (n=91) was 1.73 ± 2.50 (t(90)=6.59, p<0.00001)(Table E5 of On-Line Supplement) with a moderately large standardized effect size of 0.69. Statistically robust improvements in function were observed for all

FOSQ subscale domains. While the standard effect sizes varied, all were at least moderately large (Table E5 of On-Line Supplement). Significant improvements in the cross-over cohort were also observed in ESS score with a change of 2.3 ± 4.0 ($p < 0.001$), all component scores of the SF36 (p values < 0.020), and several domains of the POMS (Fatigue, Confusion-Bewilderment, Vigor, and Total Mood Disturbance; p values < 0.003). The mean change in the number of PVT lapses was -3.93 ± 13.46 (SD) ($p = 0.011$). No significant changes in BP measures following 8-wks of active treatment were observed in the cross-over cohort.

Safety Analysis

Online Supplement Table E2 summarizes the overall safety experience in the two intervention groups. There were few important adverse events with no significant group differences.

DISCUSSION

To our knowledge, this multi-site, double-blind, RCT presents the findings from the largest placebo-controlled investigation of the efficacy of CPAP treatment in sleepy patients with milder OSA. Sleepy patients with mild and moderately severe OSA had greater functional improvement after eight weeks of CPAP therapy compared to sham CPAP. The group difference in change in FOSQ Total score, ESS, Physical Component of the SF36, and Total Mood Disturbance were highly significant and clinically relevant as indicated by the effect size. Of note is that the mean change in FOSQ Total Score was quite similar to the difference in this score between CPAP and usual care/placebo in studies that have included a wide spectrum of disease

severity.(12) As a multisite study conducted at large and smaller clinical practice sites, our results are highly generalizable. Moreover, our sample reflects the typical age associated with OSA and had almost equal representation of genders. Our protocol was designed to have the least impact on the routine care provided at the clinical centers; thus, we believe that our results have high external validity and are applicable to outcomes associated with the management of CPAP-treated patients at most sleep centers.

A major strength of our study is the use of sham CPAP for the placebo intervention. The few studies that have explored the impact of CPAP treatment in milder OSA have employed conservative therapy or placebo tablets as controls.(10, 20-23) There has been criticism that these controls make it difficult to blind the participants and research personnel and do not provide the participants with the same experience as CPAP. (24) In response, we used as our control sham CPAP that does not deliver effective pressure, adversely affect sleep, or reduce AHI.(19) Comparison of the PSGs performed at baseline with and without sham CPAP did show changes in some secondary PSG measurements.(19) However, the lack of significant change in any functional outcome measure in the sham-CPAP group provides strong evidence that these PSG differences were not of clinical significance. Sham CPAP allowed a true efficacy comparison with active CPAP, especially related to subjective assessments.(24, 25) Our finding that active CPAP treatment compared to placebo enhanced daily functioning is consistent with previous RCTs conducted primarily in those with moderate to severe OSA.(9-12)

Results of recent meta-analyses of CPAP RCTs(9, 10) prompted the recommendation to treat moderate to severe OSA as a practice standard.(8) However, lacking conclusive evidence in those with more mild disease, the American Academy of Sleep Medicine indicated that CPAP is an optional patient-care strategy for enhancing quality of life in this population.(8) The improvement we found in functional status in sleepy patients with milder OSA is consistent with studies of those with more severe disease and supports the application of CPAP therapy as standard in patients with milder OSA who have symptoms of daytime sleepiness.(9)

As the primary manifestation of OSA, daytime sleepiness has been the most common treatment outcome investigated. In a meta-analysis of seven RCTs of the impact of CPAP on self-rated sleepiness in mild sleep apnea, Marshall and colleagues reported that ESS scores were significantly improved following CPAP treatment by 1.2 points (95% CI 0.5 to 1.9, p = 0.001), after controlling for placebo effects.(26) These findings are consistent with our results showing an adjusted difference in mean change between the treatment arms of -1.8 (95% CI -0.75 to -2.82, p = 0.001) indicating that participants perceived greater alertness with CPAP treatment. We believe that our larger sample size and lower average dropout rate compared to the studies included in the meta-analysis accounts for our more robust findings.

Study Limitations

A concern was the mean duration of daily CPAP treatment. Despite a protocol to promote CPAP use through pre-treatment education followed by weekly contact that included troubleshooting and motivation (see on-line supplement), our mean daily CPAP use was only 4.0 ± 2.0 and 3.1 ± 2.1 hours/day in the active CPAP and sham

CPAP groups, respectively. We did not achieve the desired six hours or greater nightly use, nor did we get equal exposure to intervention between the two groups. Previous RCTs also report mean use of < 5 hours.(9, 11) Despite the statistically significant improvement in daytime sleepiness, at the end of the treatment period 71% of the active treatment arm had an Epworth Sleepiness Scale total score large than the normal value of 10(13). Eighty three percent of the sham group self-reported daytime sleepiness. The improvement in the active group relative to sham was statistically significant (chi-square p=0.03). The persistence of daytime sleepiness on treatment is not novel to this study and has been previously reported.(27, 28,29) It is speculated that the residual sleepiness evident in our study may be related to the less than optimal nightly duration of CPAP use of 4.0 ± 2.0 hrs. rather than the desired >6 hrs. of use.(29) The lower mean daily adherence to sham CPAP than active CPAP in our study was likely associated with the perception of decreased benefit. As the duration of treatment use in our study is similar to the 4-hr average in the clinical setting,(9) expectations for clinical outcomes for milder OSA would be consistent with our findings. Moreover, although we showed that the FOSQ Total score improves linearly with increasing hours of use (i.e., more is better), some benefit was achieved even with relatively low usage time.(29)

Conclusion

This multi-site, double-blind RCT is the first placebo controlled study using sham CPAP in sleepy patients with mild to moderate OSA and demonstrates improved quality of life and symptom reduction with CPAP treatment. It remains unclear whether those with milder OSA who do not report daytime sleepiness would experience similar benefits.

Given the high prevalence of OSA in the general public, this study importantly suggests significant value in treating sleepy patients with the mild to moderate disease. While other forms of treatment are available, such as dental appliances, CPAP is the primary treatment for OSA. Our results demonstrate that CPAP therapy for sleepy patients with milder OSA can confer significant health benefits.

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References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. *American journal of respiratory and critical care medicine* 2002;165:1217-1239.

2. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, Nieto FJ, Rosenberg CE. Relation of sleepiness to respiratory disturbance index: The sleep heart health study. *American journal of respiratory and critical care medicine* 1999;159:502-507.

3. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. The report of an american academy of sleep medicine task force. *Sleep* 1999;22:667-689.

4. Selim B, Won C, Yaggi HK. Cardiovascular consequences of sleep apnea. *Clin Chest Med* 2010;31:203-220.

5. Ellen RL, Marshall SC, Palayew M, Molnar FJ, Wilson KG, Man-Son-Hing M. Systematic review of motor vehicle crash risk in persons with sleep apnea. *J Clin Sleep Med* 2006;2:193-200.

6. Ulfberg J, Carter N, Talback M, Edling C. Excessive daytime sleepiness at work and subjective work performance in the general population and among heavy snorers and patients with obstructive sleep apnea. *Chest* 1996;110:659-663.

7. Lui MM, Ip MS. Disorders of glucose metabolism in sleep-disordered breathing. *Clinics in chest medicine* 2010;31:271-285.

8. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, Boehlecke B, Brown TM, Coleman J, Jr., Friedman L, Kapen S, Kapur VK, Kramer M,

Lee-Chiong T, Owens J, Pancer JP, Swick TJ, Wise MS. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006;29:375-380.

9. Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 2006;29:381-401.

10. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006;3:CD001106.

11. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, Jagia P, Kumar A. Cpap for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 2011;365:2277-2286.

12. McDaid C, Griffin S, Weatherly H, Duree K, van der Burgt M, van Hout S, Akers J, Davies RJ, Sculpher M, Westwood M. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: A systematic review and economic analysis. *Health Technol Assess* 2009;13:iii-iv, xi-xiv, 1-119, 143-274.

13. Johns MW. Sensitivity and specificity of the multiple sleep latency test (mslt), the maintenance of wakefulness test and the epworth sleepiness scale: Failure of the mslt as a gold standard. *J Sleep Res* 2000;9:5-11.

14. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835-843.

15. Ware JE, Snow KK, Kosinski M, Gandek B. Sf 36 health survey. Manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1990.

16. Dinges D, Powell J. Microcomputer analyses of performance on a portable, simple visual rt task during sustained operations. *Beh Res Meth, Instr,& Comp* 1985;17:652-655.

17. McNair DM, Lorr M, Druppleman LF. Eits manual for the profile of mood states. San Diego: Educational and Industrial Test Services; 1971.

18. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J, Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Loube DL, Owens J, Pancer JP, Wise M. Practice parameters for the indications for polysomnography and related procedures: An update for 2005. *Sleep* 2005;28:499-521.

19. Rodway GW, Weaver TE, Mancini C, Cater J, Maislin G, Staley B, Ferguson KA, George CF, Schulman DA, Greenberg H, Rapoport DM, Walsleben JA, Lee-Chiong T, Kuna ST. Evaluation of sham-cpap as a placebo in cpap intervention studies. *Sleep* 2010;33:260-266.

20. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, Trinder J, Saunders NA, Douglas McEvoy R, Pierce RJ. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *American journal of respiratory and critical care medicine* 2002;165:773-780.

21. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, Pierce RJ. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *American journal of respiratory and critical care medicine* 2004;170:656-664.

22. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of cpap therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax* 1997;52:114-119.

23. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. *American journal of respiratory and critical care medicine* 1999;159:461-467.

24. Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: A systematic review of the research evidence. *British Medical Journal* 1997;314:851-860.

25. Jenkinson C, Davies RJO, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised prospective parallel trial. *The Lancet* 1999;353:2100-2105.

26. Marshall NS, Barnes M, Travier N, Campbell AJ, Pierce RJ, McEvoy RD, Neill AM, Gander PH. Continuous positive airway pressure reduces daytime sleepiness in mild to moderate obstructive sleep apnoea: A meta-analysis. *Thorax* 2006;61:430-434.

27. Schwartz JR, Hirshkowitz M, Erman MK, Schmidt-Nowara W. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea: A 12-week, open-label study. *Chest* 2003;124:2192-2199.

28. Bittencourt LR, Lucchesi LM, Rueda AD, Garbuio SA, Palombini LO, Guilleminault C, Tufik S. Placebo and modafinil effect on sleepiness in obstructive sleep apnea. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:552-559.

29. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;30:711-719.

Figure Legends

Figure 1: Flowchart of the study profile. Of the 385 participants screened and consented, 281 were randomized, 42 withdrew prior to any exposure to active or sham CPAP. These unexposed participants, although randomized, were excluded from all analyses. There were 239 randomized and exposed participants (N = 121 active and N = 118 sham CPAP).

Figure 2: The mean (SD) FOSQ Total score by treatment group in the primary efficacy cohort before and after the 8 week treatment period.

TABLE 1. PARTICIPANT CHARACTERISTICS AT BASELINE RANDOMIZED AND EXPOSED

Variable (Mean or %)	Participants randomized to active CPAP n=121	Participants randomized to sham CPAP n=118	p-value[1]	Effect Size
Age (years)	49.5 ± 10.9	51.7 ± 11.9	0.13	-0.54
Percent males	54.5	62.7	0.20*	N/A
Percent African Americans	15.7	16.9	0.80*	N/A
Body mass index (kg/m^2)	33.2 ± 6.3	34.2 ± 7.8	0.42	-0.14
Weight (lbs.)	212.9 ± 44.3	223.5 ± 22.2	0.32	-0.30
Apnea-hypopnea index (events/hr w/dsats > 3%)	12.8 ± 6.4	12.5 ± 6.5	0.69	0.05
Arousal index (events/hr)	33.2 ± 14	30.4 ± 11.8	0.09	0.22
O_2 desaturation index (events/hr)	14.3 ± 6.8	13.9 ± 6.8	0.67	0.06
FOSQ Total score	13.91 ± 3.0	14.41 ± 2.8	0.18	-0.17
General productivity	2.90 ± 0.7	3.01 ± 0.6	0.21	-0.17
Vigilance	2.5 ± 0.7	2.62 ± 0.6	0.07	-0.18
Social outcome	3.09 ± 0.7	3.02 ± 0.8	0.48	0.11
Activity level	2.58 ± 0.7	2.73 ± 0.7	0.09	-0.23
Intimacy & sexual relationships	2.83 ± 1.0	3.05 ± 0.9	0.11	-0.23
SF-36 score				
Physical activity component	41.81 ± 10.8	42.26 ± 10.2	0.76	-0.04

Mental health component	42.92 ± 11.06	46.04 ± 10.4	0.04	-0.29
Epworth total score	15.21 ± 3.37	14.66 ± 3.05	0.20	0.17
PVT transformed lapses	18.49 ± 29.59	12.94 ± 21.21	0.12	0.19
POMS Total Mood Disturbance	25.7 ± 26.3	17.9 ± 27.5	0.03	0.29
Mean arterial BP	92.5 ± 8.2	91.6 ± 8.8	0.46	0.11
Systolic BP – Day	124.5 ± 13.7	124.4 ± 10.9	0.94	0.00
Diastolic BP - Day	76.2 ± 10.1	74.8 ± 9.6	0.36	0.14

FOSQ = Functional Outcomes of Sleep Questionnaire; PVT = Psychomotor Vigilance Task; SF-36 = Short Form 12; CES-D = Center for Epidemiologic Studies Depression Scale; MAP Index = Multivariable Apnea Prediction Index. 1. t-tests for differences; * Fisher's Exact test

TABLE 2. THE UNADJUSTED MEAN CHANGES IN FOSQ TOTAL AND COMPONENT SCORES FOLLOWING THE 8-WEEK INTERVENTION WITH ACTIVE VERSUS SHAM CPAP.

Variable	Active CPAP group n = 113		Sham CPAP group n = 110	
	Mean change	P value[1]	Mean change ± SD	P Value[1]
FOSQ Total Score	0.98 ± 2.89	0.0005	-0.14 ± 2.61	0.57
General Productivity	0.20 ± 0.62	0.0007	0.00 ± 0.61	0.97
Vigilance	0.16 ± 0.77	0.03	-0.12 ± 0.81	0.14
Social Outcome	0.08 ± 0.83	0.34	- 0.02 ± 0.78	0.86
Activity Level	0.26 ± 0.70	0.0001	-0.05 ± 0.56	0.32
Intimacy/Sexual Relationships	0.09 ± 1.11	0.42	-0.14 ± 1.06	0.22

[1] Paired t-tests
[2] P-value from Type II sum of squares estimated by way of analysis of covariance. To produce site weighted comparisons the ANCOVA model included main effects for treatment group, site, and pre treatment baseline value.

TABLE 3. CHANGES FROM PRE-TREATMENT BASELINE TO THE FINAL TREATMENT PERIOD IN THE ITT SAMPLE. PRIMARY AND SUPPORTING TESTS FOR EFFICACY

FOSQ Domain	Active Sample Size	Sham Sample Size	Active Adjusted Mean Change[1]	Sham Adjusted Mean Change[1]	Adjusted Difference in Mean Changes (SE)[1]	P-value[2]	Lower and Upper Bounds of 95% CI for Differences in Mean Changes	
Total Score	113	110	0.89	-0.06	0.95 (0.34)	0.006	0.27	1.62
General Productivity	113	110	0.18	0.02	0.17 (0.07)	0.026	0.02	0.31
Vigilance	113	110	0.12	-0.08	0.20 (0.10)	0.043	0.01	0.38
Social Outcome	113	108	0.09	-0.04	0.13 (0.10)	0.179	-0.06	0.33
Activity Level	113	110	0.23	-0.02	0.25 (0.08)	0.002	0.09	0.40
Intimacy/Sexual Relationships	110	95	0.06	-0.10	0.15 (0.15)	0.305	-0.14	0.45

[1] Adjusted mean changes and adjusted differences in mean changes were estimated as site-total-sample-size weighted values controlling for treatment group differences in mean pre-treatment baseline values. Individual baseline values were used for individual FOSQ component scores.

[2] P-value from Type II sum of squares estimated by way of analysis of covariance. To produce site weighted comparisons the ANCOVA model included main effects for treatment group, site, and pre treatment baseline value.

TABLE 4. FOSQ TOTAL SCORE SUMMARY STATISTICS BY TREATMENT GROUP IN THE INTENT-TO-TREAT[1] AND PER PROTOCOL SAMPLES[3]

			Pre Treatment Baseline FOSQ Total Score			Final Treatment Period[2] FOSQ Total Score			Change from Baseline			Percent Change from Baseline		
Sample	**Treatment**	**N**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Intent-to-treat[4]	Active	113	13.92	3.02	14.39	14.89	3.32	15.29	.98	2.89	.90	9.1%	23.3%	5.8%
	Sham	110	14.41	2.75	14.70	14.27	2.96	14.79	-.14	2.61	-.21	.6%	19.2%	-1.3%
LOCF Disabled	Active	105	13.96	2.98	14.48	15.19	3.07	15.40	1.23	2.61	1.13	11.0%	22.2%	7.3%
	Sham	101	14.40	2.76	14.62	14.41	2.82	14.79	.01	2.40	-.19	1.7%	18.3%	-1.2%
Per Protocol[5]	Active	52	13.07	3.15	13.61	14.75	3.59	15.39	1.68	2.88	1.49	15.3%	26.2%	11.4%
	Sham	41	13.93	2.66	13.95	14.25	2.86	14.54	.32	2.66	.25	4.0%	19.7%	1.9%

Notes:

[1]The Intent-to-Treat Sample includes all randomized patients exposed to active CPAP or sham CPAP treatment during the post-randomization treatment period.

[2]Final Treatment period FOSQ endpoints are defined at Week 8 or last available among Weeks 1-7 based on available Smartcard data.

[3]The Per Protocol (PP) Sample includes randomization patients meeting criterion for inclusion in the ITT Sample who also meet CPAP compliance criterion and who have no major clinically significant protocol deviations during the post-randomization treatment period. Missing endpoint values are not imputed for analyses involving the PP Sample.

[4]Primary efficacy analyses were performed in the Intent-to-Treat Sample.

[5]Secondary efficacy analyses were performed in the Per Protocol Sample (PP).

Figure 1

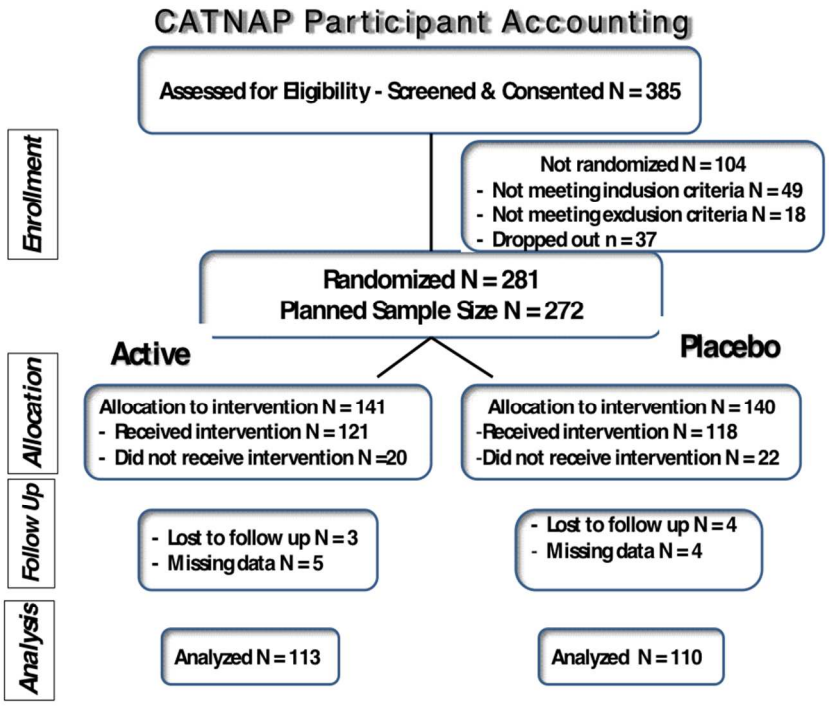
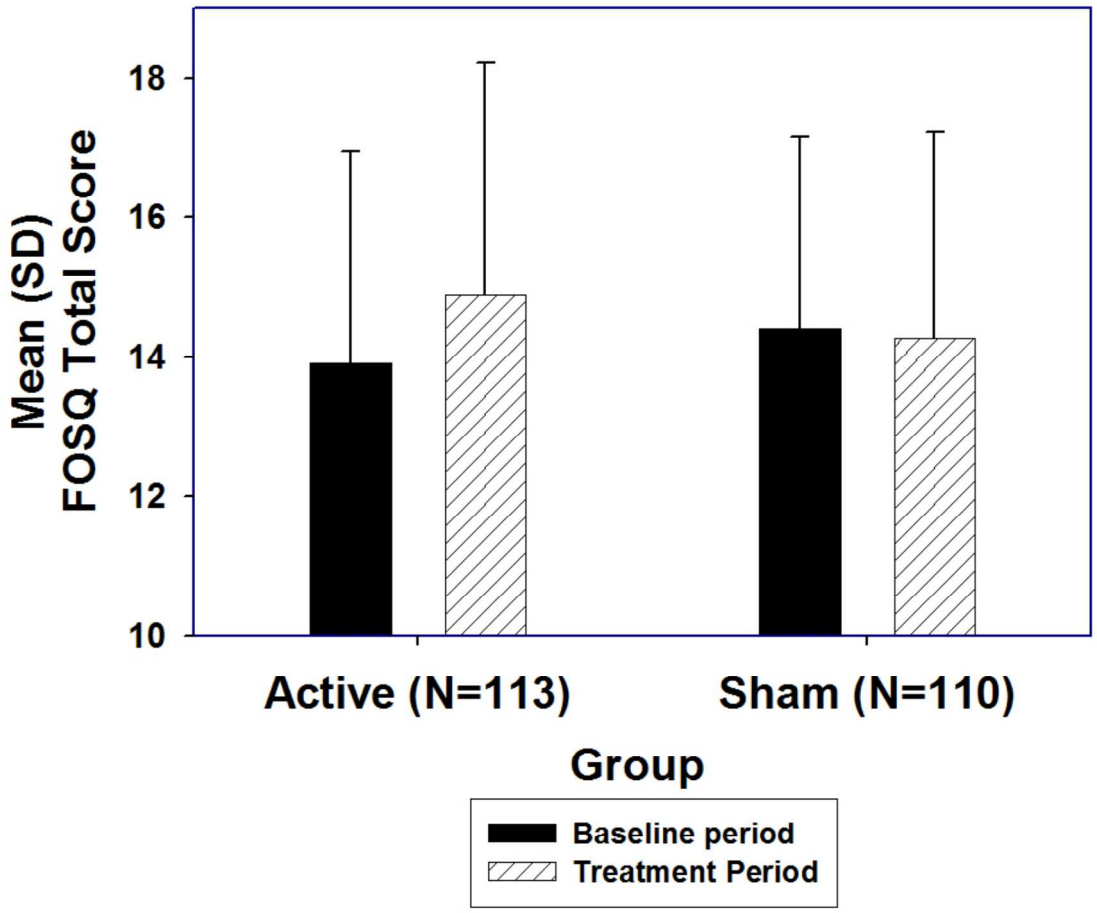


Figure 2


Mean (SD)
FOSQ Total Score
18
16
14
12
10
Active (N=113)
Sham (N=110)
Group
Baseline period
Treatment Period

CPAP Treatment of Sleepy Patients with Milder OSA: Results of the CATNAP Randomized Clinical Trial

Web Supplement

Reading Level Assessment

The ability to write and read in English at the fifth grade level was evaluated using a brief passage regarding the risks of daytime sleepiness written at the fifth grade reading level as determined by the Flesch-Kincaid assessment.(1) All participants were asked to read the passage as part of the informed consent process and respond to a series of questions evaluating their comprehension.

Primary Endpoint

Functional Outcome of Sleep Questionnaire (FOSQ): FOSQ is a validated 30-item, self-report, disease-specific, functionally-based gold standard measure designed to assess the impact of disorders of excessive sleepiness on functional status.(2) Factor analysis of the FOSQ was conducted with 133 subjects seeking medical attention at two different sleep disorders centers and 20 normal controls (to enhance the variability of responses).(2) This analysis yielded five factors (subscales): Activity Level, Vigilance, Intimacy and Sexual Relationships, General Productivity, and Social Outcome. Internal reliability of the measure was excellent for both the subscales (α=0.70 to α=0.92) and for the total scale (α=0.96). Test-retest reliability of the FOSQ yielded coefficients ranging from r=0.74 to r=0.88 for the five subscales, and r=0.91 for the total measure. The normal value on the FOSQ Total score is 17.9, determined in a sample of normal individuals free of sleep disorders as verified by polysomnograpy.(3-5)**Secondary Endpoints**

Epworth Sleepiness Scale (ESS): The ESS is a self administered questionnaire that evaluates subjective sleepiness.(6) This scale rates the likelihood of falling asleep in eight soporific situations using a four-point Likert scale ranging from never dozing to high chance of dozing. The ESS significantly correlates with the frequency of apneas and has been used extensively in clinical assessment and sleep apnea research.

Psychomotor Vigilance Task (PVT): The PVT is an objective assessment of sleepiness and measures decrements in neurobehavioral performance due to sleepiness, i.e., ability to sustain attention and respond in a timely manner to salient signals.(7) The PVT yields five highly informative metrics on the capacity for sustained attention and vigilance performance: frequency of lapses, duration of lapse domain, optimum response time, vigilance decrement function, false response frequency. We applied this conceptually valid, relatively short duration, reliable task with known psychometric properties and minimal practice/learning curves to document attentional lapses (response times > 500 msec) in performance. A component of the PVT, the Visual Analog Scale (VAS) asks respondents to indicate on a line the location that best reflects their degree of sleepiness with the anchors “not sleepy”, “very sleepy”.

Medical Outcomes Study Short Form-36 (SF-36): The SF-36 is a 36-item questionnaire that assesses eight health concepts: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.(8)

Profile of Mood States (POMS): The POMS measures self-reported mood during the daytime.(9) The POMS is a reliable and valid measure of mood states that consists

of 65 adjectives on which subjects' rate themselves as they feel "today" using a five-point scale. There are six mood or affective states on this test derived through factor analysis: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. There is also a summary Total Mood Disturbance (TMD) score that gives a Total estimate of affective state. The POMS test requires 3 to 5 minutes for most subjects to complete.

Ambulatory Blood Pressure: Ambulatory blood pressure was measured using the Spacelabs™ ambulatory blood pressure cuff and monitoring system. Systolic blood pressure (BP), diastolic BP, and 48-hour mean ambulatory arterial BP during the day, during the night and their difference were measured.

Diagnostic and Titration Polysomnography and Scoring

To standardize data collection across sites, the same polysomnograph (PSG) signals were recorded at each site during both the diagnostic and sham-CPAP PSGs including: electroencephalograms (C3M2, C4M1, O2M1), bilateral electrooculograms, electromyograms of the chin muscles and right and left anterior tibialis, movement of the rib cage and abdomen (piezoelectric crystal), oxygen saturation (SaO2) by pulse oximetry, electrocardiogram (Lead 1), and body position. For the diagnostic PSG, nasal pressure (ProTech PTAF2™) was the surrogate airflow signal, and mask pressure (ProTech PTAF2™) was used as the airflow signal on the sham-CPAP studies. The only equipment that was standardized across all sites was the amplifier for the nasal pressure signal (Pro-Tech Services, Inc., Mukilteo, WA). The airflow signal from the CPAP machine could not be used since the large expiratory leak and orifice restrictor in the sham-CPAP circuit prevented the signal from being received by the machine's

sensors. Each site adhered to uniform criteria for signal processing (e.g., digitization rates and alternating current [AC] filters).

Polysomnographic files were electronically transmitted to the central scoring laboratory at the University of Pennsylvania by means of the CATNAP web portal or File Transfer Protocol (FTP) for centralized manual, computer software-assisted scoring (Sandman NT™ software [Embla, Ottawa, Ontario, Canada]). Three of the clinical sites recorded the PSGs using software different from that used by the scoring lab. In order for these recordings to be analyzed, the files were converted into European Data Format prior to being transmitted to the scoring lab. Since electronic tags on the files were lost when the files were converted to European Data Format, the technologists used a standardized PSG event log to record events during the studies.

Sleep stages were characterized by Rechtschaffen and Kales criteria.(10) Arousals were characterized by the AASM criteria.(11) An arousal was associated with a respiratory event if it began within 3 seconds of the termination of the event. Apneas were identified if the airflow signal was flat or nearly flat (i.e., below at least 10% of baseline) and the decrease lasted for > 10 seconds. Apneas associated with respiratory effort were scored as obstructive apneas. Apneas that were not associated with respiratory effort were scored as central apneas. Mixed apneas were scored as obstructive apneas. A decrease in amplitude of a respiratory signal for at least 10 seconds that was associated with a greater than 3% oxygen desaturation was scored as a hypoponea. The AHI was calculated as the mean number of apneas and hypopneas per hour of sleep.

Placebo Device and Sham Titration

The sham CPAP apparatus (RemStar Pro, Respironics, Inc., Murrysville, PA) consisted of an enlarged air leak incorporated into the exhalation valve (WhisperSwivel®, Respironics, Inc.) between the mask and the CPAP tubing and an orifice restrictor in the CPAP circuit.(12) When fully assembled, this modification in the exhalation valve was not visibly perceptible. Participants randomized to the placebo intervention were fitted with one of the following nasal mask interfaces: Comfort Gel, Comfort Classic, Comfort Select, and Profile Lite (Respironics, Inc.) During the sham CPAP PSG, the technologists used the sleep centers' remotely controlled CPAP machines as the sham-CPAP device to avoid the possibility of unblinding participants. The laboratory CPAP machine was converted into a sham device by inserting the orifice restrictor into the circuit at the point where the CPAP tubing connected to the machine. With the machine set at 10 cm H2O throughout the night and the sham expiratory valve and external orifice resistor in the circuit, the pressure at the mask interface was less than 1 cm H2O. The sham-CPAP apparatus (Respironics, Inc.) distributed to the participants for home use had the same circuit as that used during the PSG with sham-CPAP, except that the orifice restrictor was contained in the CPAP machine so that it was not visible and the machine looked identical to that used by participants randomized to active CPAP treatment.

CPAP Set-up and Education

Before CPAP set-up by the PSG technologist, all participants received a standardized education session with their bed partner designed to improve their CPAP adherence. They also received data cards for their device that documented mask on time. Each participant received an educational brochure, which was reviewed by the

unblinded technologist. In addition to motivational content to promote adherence, the brochure covered what CPAP was, why regular use was important, care and daily cleaning of the mask, how to troubleshoot mask-related problems, how to perform weekly cleaning of the mask and the device, care and cleaning of the humidifier, and general care of the device. In conjunction with reviewing the brochure, the unblinded technologist also demonstrated the described techniques using an unpowered unit. Participants received weekly telephone calls to encourage device use.

Inclusion/exclusion Criteria

The determination of alcohol abuse based on the CAGE questionnaire score was changed after the study commenced to better reflect the conceptual definition.

Randomization and Masking

Participants and all members of the research team were blinded to intervention except for the site polysomnographic technologist who performed the polysomnogram and CPAP set-ups based on the assigned intervention. Study personnel at the PSG Reading Center who scored and interpreted the polysomnograms were also unblinded.

Randomisation was performed by computer centrally for each site by the Data Coordinating Center at the University of Pennsylvania. For enrolled participants, a computer-generated randomization number was obtained by the research coordinator and communicated to the PSG technologist who matched it with a sealed envelope, kept in a locked box, containing the treatment allocation. The appropriate device was then selected by the PSG technologist who distributed it to the research coordinator for distribution in a sealed black bag.

Role of the Funding Source

The sponsors of this study had no role in developing the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit this study for publication.

Statistical Analysis

Age (<60, ≥ 60), race (white, other), and sex main effects and interactions with treatment as well as group differences in baseline FOSQ Total score and baseline factors with significant group differences found to be associated with change in FOSQ Total score were applied as covariates in the analysis of covariance. Interim analysis for safety was performed when half of the sample had completed the protocol.

Weekly FOSQ score

FOSQ data were obtained weekly from the smartcard download. These data were used in LOCF to provide a follow up FOSQ Total score for participants who failed to return for their final 8-wk assessment. Table E1 displays the weekly data for each group. There were significant difference between weeks within group ($F_{86.39}$, $p<0.001$), but no differences between groups overall ($F_{0.14}$, $p = 0.714$) an no interaction of group by week ($F_{1.69}$, $p = 0.097$).

Adverse Events

There were few important adverse events and no significant differences between groups (Table E2).

References

1. KINCAID J, R F, R R, B C. Derivation of new readabiity formulas (automated reliability index, fog count and flesch reading ease formula) for navy enlisted personnel. MEMPHIS, TENN: NAVAL AIR STATION; 1975.

2. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835-843.

3. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI. Relationship between hours of cpap use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;30:711-719.

4. Wang D, Teichtahl H, Goodman C, Drummer O, Grunstein RR, Kronborg I. Subjective daytime sleepiness and daytime function in patients on stable methadone maintenance treatment: Possible mechanisms. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2008;4:557-562.

5. Chasens ER, Ratcliffe SJ, Weaver TE. Development of the fosq-10: A short version of the functional outcomes of sleep questionnaire. *Sleep* 2009;32:915-919.

6. Johns MW. Sensitivity and specificity of the multiple sleep latency test (mslt), the maintenance of wakefulness test and the epworth sleepiness scale: Failure of the mslt as a gold standard. *J Sleep Res* 2000;9:5-11.

7. Dinges D, Powell J. Microcomputer analyses of performance on a portable, simple visual rt task during sustained operations. *Beh Res Meth, Instr,& Comp* 1985;17:652-655.

8. Ware JE, Snow KK, Kosinski M, Gandek B. Sf 36 health survey. Manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1990.

9. McNair DM, Lorr M, Druppleman LF. Eits manual for the profile of mood states. San Diego: Educational and Industrial Test Services; 1971.

10. Rechtschaffen A, Kales A. A manuel of standardized terminology, techniques and scoring system for sleep stages of human subjects. UCLA, Los Angeles: Brain Information Service/Brain Research Institute; 1968.

11. Eeg arousals: Scoring rules and examples: A preliminary report from the sleep disorders atlas task force of the american sleep disorders association. *Sleep* 1992;15:173-184.

12. Rodway GW, Weaver TE, Mancini C, Cater J, Maislin G, Staley B, Ferguson KA, George CF, Schulman DA, Greenberg H, Rapoport DM, Walsleben JA, Lee-Chiong T, Kuna ST. Evaluation of sham-cpap as a placebo in cpap intervention studies. *Sleep* 2010;33:260-266.

SUPPLEMENTARY TABLE E1. WEEKLY FOSQ TOTAL SCORE FOR ACTIVE AND SHAM CPAP GROUPS

Week	N	MEAN ± SD	N	MEAN ± SD
	ACTIVE CPAP*		SHAM CPAP*	
1	30	7.09 ± 3.68	25	6.21 ± 1.96
2	44	11.21 ± 5.13	44	11.56 ± 4.34
3	64	13.09 ± 4.32	63	13.58 ± 2.87
4	69	13.62 ± 4.22	73	13.34 ± 3.42
5	71	13.91 ± 4.05	81	14.11 ± 3.40
6	79	14.57 ± 3.97	76	13.53 ± 3.65
7	70	13.96 ± 3.95	78	13.59 ± 3.58
8	74	14.11 ± 3.99	76	14.12 ± 2.98
9 (FOLLOW UP)	81	14.45 ± 3.94	73	13.91 ± 3.33

*Within group effect by week $p<0.0001$

SUPPLEMENTARY TABLE E2. SUMMARY OF CLINICAL ADVERSE EXPERIENCES DURING THE POST-RANDOMIZATION TREATMENT PERIOD PRIMARY SAFETY SAMPLE[1]

Characteristic of Events	**Active N = 121**		**Sham N = 118**		
Number (%) of Patients	*n*	%	*n*	%	*p* value[4]
With No Adverse Experiences	28	23.1	26	22.0	
With One or More Adverse Experiences	93	76.9	92	78.0	.88
With Study-Related Adverse Experiences[2]	46	38.0	42	35.6	.79
With Device-Related Adverse Experiences[3]	50	41.3	39	33.1	.23
With Serious Adverse Experiences	5	4.1	9	7.6	.28
-With Serious Study-Related Adverse Experiences[2]	0	0	1	.8	.49
-With Serious Device-Related Adverse Experiences[3]	0	0	1	.8	.49
Who Died	0	0	0	0	1.00
Discontinued Study Due to an Adverse Experience	0	0	0	0	1.00
Discontinued Treatment Due to an Adverse Experience	1	.8	0	0	1.00
Discontinued Study or Treatment Due to an Adverse Experience	1	.8	0	0	1.00
-Discontinued Study or Treatment Due to a Study-Related Adverse Experiences[2]	1	.8	0	0	1.00

-Discontinued Study or Treatment Due to a Device-Related Adverse Experiences[3]	1	.8	0	0	1.00
-Discontinued Study or Treatment Due to a Serious Adverse Experience	0	0	0	0	1.00

Notes:

[1]The Primary Safety Sample includes all patients exposed to CPAP or Sham treatment status.

[2]Study-related includes possibly, probably, definitely, and those with unknown/undetermined

(documented exposure of at least 20 minutes) during the post-randomization.

[3]Device-related includes possibly, probably, definitely, and those with unknown/undetermined status.

[4]Fisher's Exact 2-tailed test.

SUPPLEMENTARY TABLE E3A. NUMBER (%) OF RANDOMIZED AND EXPOSED PARTICIPANTS EXPERIENCING A LIFE TIME MEDICAL CONDITION BY TREATMENT

	Active		Sham		
Factor	**n**	**%**	**n**	**%**	**p-value[1]**
Any other life time medical condition	118	97.5	110	93.2	.13
No other life time medical condition	3	2.5	8	6.8	.13
More than one other medical condition	87	71.9	84	71.2	1
Diabetes	16	13.2	19	15.4	.71
Chronic Bronchitis	2	1.7	5	4.3	.27
Emphysema/COPD	1	.8	4	3.4	.21
Asthma	16	13.2	21	17.9	.37
Other Lung Disease	6	5.0	5	4.3	1
High Blood Pressure	49	40.5	46	39.3	.90
Pulmonary Hypertension	0	0	0	0	NVT
Angina	5	4.1	7	6	.57
Heart Attack	3	2.5	5	4.3	.49

Arrhythmia	8	6.6	17	14.5	.06
Heart Failure	2	1.7	2	1.7	1
Syncope	11	9.1	2	1.7	.02
Stroke	6	5	4	3.4	.75
Other Heart Disease	11	9.1	5	4.3	.20
Thyroid Disease	13	10.7	12	10.3	1
Sinus Disease	13	10.7	19	16.2	.26
Hay Fever	21	17.4	27	23.1	.33
Deviated Nasal Septum	15	12.4	13	11.1	.84
Seizure Disorder	3	2.5	0	0	.25
Impotence	5	4.1	2	1.7	.45
Arthritis	29	24	3	28.2	.46
Depression	39	32.2	39	33.3	.89
Other Psychiatric Conditions	11	9.4	9	7.8	.82
Other Conditions	63	55.8	55	47.8	.24
Notes: [1]Fisher's Exact Test; NVT-No valid test					

SUPPLEMENTARY TABLE E3B. NUMBER (%) OF RANDOMIZED AND EXPOSED PARTICIPANTS EXPERIENCING A CURRENT MEDICAL CONDITION BY TREATMENT GROUP

	Active		Sham		
Factor	**n**	**%**	**n**	**%**	**p-value[1]**
Any current medical condition	116	95.9	106	89.8	.08
No other current medical condition	5	4.1	12	10.2	.08
More than one current medical condition	76	62.8	77	65.3	.79
Diabetes	15	12.4	18	15.3	.58
Chronic Bronchitis	2	1.7	2	1.7	1
Emphysema/COPD	1	.8	3	2.5	.37
Asthma	13	10.7	16	13.6	.56
Other Lung Disease	2	1.7	3	2.5	.68
High Blood Pressure	49	40.5	45	38.1	.79
Pulmonary Hypertension	0	0	0	0	NVT
Angina	3	2.5	5	4.2	.50
Heart Attack	2	1.7	2	1.7	1
Arrhythmia	5	4.1	12	10.	.08

				2	
Heart Failure	1	.8	2	1.7	.62
Syncope	2	1.7	0	0	.50
Stroke	2	1.7	0	0	.50
Other Heart Disease	6	5	1	.8	.12
Thyroid Disease	11	9.1	10	8.5	1
Sinus Disease	12	9.9	17	14.4	.33
Hay Fever	21	17.4	27	22.9	.33
Deviated Nasal Septum	13	10.7	10	8.5	.66
Seizure Disorder	1	.8	0	0	1
Impotence	5	4.1	2	1.7	.45
Arthritis	29	24	32	27.1	.66
Depression	31	25.6	33	28	.77
Other Psychiatric Conditions	10	8.3	7	5.9	.62
Other Conditions	61	50.4	47	39.8	.12
Notes: [1]Fisher's Exact Test; NVT-No valid test					

SUPPLEMENTTABLE E4 NUMBER (%) OF RANDOMIZED AND EXPOSED PARTICIPANTS WITH SPECIFIC CONCOMITANT MEDICATIONS BY GROUP.

	Active (n=121)		Sham (n=118)	
	n	%	n	%
With no concomitant medications	3	2.5	8	6.8
With one or more concomitant medications	118	97.5	110	93.2
AA/LIVER-SPLEEN SHEEP EXTRACT	1	0.8	0	0.0
ACETAMINOPHEN	51	42.1	55	46.6
ACETAMINOPHEN WITH CODEINE	6	5.0	8	6.8
ACETAMINOPHEN/CAFFEINE	1	0.8	1	0.8
ACETAMINOPHEN/CHLOR-MAL	0	0.0	1	0.8
ACETAMINOPHEN/DP-HYDRAM HCL	2	1.7	1	0.8
ACIDOPHILUS/BIFIDO LONGUM	1	0.8	0	0.0
ACITRETIN	0	0.0	1	0.8
ALBUTEROL	11	9.1	10	8.5
ALBUTEROL SULFATE	1	0.8	2	1.7
ALBUTEROL SULFATE/IPRATROPIUM	0	0.0	1	0.8
ALENDRONATE SODIUM	0	0.0	1	0.8
ALLERGENIC EXTRACTS	0	0.0	1	0.8
ALLOPURINOL	3	2.5	5	4.2
ALPRAZOLAM	4	3.3	1	0.8
AMILORIDE/HYDROCHLOROTHIAZIDE	1	0.8	1	0.8
AMINO ACIDS/VITAMIN B COMPLEX	0	0.0	1	0.8
AMITRIP HCL/CHLORDIAZEPOXIDE	0	0.0	1	0.8

AMITRIPTYLINE HCL	2	1.7	4	3.4
AMLODIPINE BESYLATE	9	7.4	7	5.9
AMLODIPINE BESYLATE/BENAZEPRIL	3	2.5	0	0.0
AMLODIPINE/ATORVAST CAL	0	0.0	1	0.8
AMMONIUM CH/PE/HYDROCODONE/PYR	0	0.0	1	0.8
AMOX TR/POTASSIUM CLAVULANATE	0	0.0	1	0.8
AMOXICILLIN TRIHYDRATE	2	1.7	7	5.9
ANESTHESIA TRAY	0	0.0	1	0.8
ASA/CALCIUM CARB/MAG/AL HYDROX	1	0.8	0	0.0
ASCORBATE CALCIUM	1	0.8	2	1.7
ASCORBIC ACID	4	3.3	3	2.5
ASCORBIC ACID/ZINC	0	0.0	1	0.8
ASPIRIN	28	23.1	40	33.9
ASPIRIN/ACETAMINOPHEN/CAFFEINE	6	5.0	0	0.0
ASPIRIN/CAFFEINE	0	0.0	1	0.8
ASPIRIN/CALCIUM CARBONATE/MAG	0	0.0	1	0.8
ASPIRIN/SOD BICARB/CITRIC ACID	0	0.0	1	0.8
ATENOLOL	8	6.6	7	5.9
ATENOLOL/CHLORTHALIDONE	0	0.0	1	0.8
ATORVASTATIN CALCIUM	23	19.0	22	18.6
ATOVAQUONE/PROGUANIL HCL	1	0.8	0	0.0
AZELASTINE HCL	1	0.8	2	1.7
AZITHROMYCIN	2	1.7	6	5.1
BACITRACIN	0	0.0	1	0.8
BACITRACIN/POLYMYXIN B SULFATE	0	0.0	1	0.8
BECLOMETHASONE DIPROPIONATE	0	0.0	1	0.8

BEE POLLEN	1	0.8	0	0.0
BENAZEPRIL HCL	0	0.0	1	0.8
BENZOCAINE	1	0.8	0	0.0
BENZOCAINE/MENTH/CETYLPYRD CL	0	0.0	2	1.7
BENZONATATE	3	2.5	0	0.0
BETA-CAROTENE	0	0.0	1	0.8
BETAMETHASONE VALERATE	0	0.0	2	1.7
BEVACIZUMAB	1	0.8	0	0.0
BISMUTH SUBSALICYLATE	2	1.7	5	4.2
BLACK COHOSH	1	0.8	0	0.0
BLOOD SUGAR DIAGNOSTIC	1	0.8	0	0.0
BRIMONIDINE TARTRATE	0	0.0	1	0.8
BRINZOLAMIDE	0	0.0	1	0.8
BUDESONIDE	3	2.5	0	0.0
BUDESONIDE/FORMOTEROL FUMARATE	0	0.0	1	0.8
BUPROPION HCL	8	6.6	4	3.4
BUSPIRONE HCL	2	1.7	1	0.8
CA CARBONATE/MAG OXIDE/CU/ZNOX	1	0.8	0	0.0
CA CARBONATE/MAG/VITAMIN D2	0	0.0	1	0.8
CA CARBONATE/VITAMIN D3/VIT K	2	1.7	1	0.8
CALCIUM	3	2.5	1	0.8
CALCIUM CARB/VIT D3/MINERALS	1	0.8	0	0.0
CALCIUM CARBONATE	4	3.3	3	2.5
CALCIUM CARBONATE/MULTIVIT	1	0.8	0	0.0
CALCIUM CARBONATE/VITAMIN D2	4	3.3	4	3.4
CALCIUM GLUCONATE	1	0.8	0	0.0

CALCIUM/MAGNESIUM	0	0.0	1	0.8
CANDESARTAN CILEXETIL	1	0.8	1	0.8
CANDESARTAN/HYDROCHLOROTHIAZID	1	0.8	0	0.0
CARBAMAZEPINE	2	1.7	0	0.0
CARBOXYMETHYLCELL/HYPROMELLOSE	0	0.0	1	0.8
CARBOXYMETHYLCELLULOSE SODIUM	0	0.0	3	2.5
CARTEOLOL HCL	1	0.8	0	0.0
CARVEDILOL	1	0.8	2	1.7
CASANTHRANOL/DOCUSATE SODIUM	0	0.0	2	1.7
CEFPROZIL	0	0.0	1	0.8
CEFTRIAXONE SODIUM	1	0.8	0	0.0
CEFUROXIME AXETIL	1	0.8	1	0.8
CELECOXIB	3	2.5	3	2.5
CEPHALEXIN MONOHYDRATE	0	0.0	2	1.7
CETIRIZINE HCL	3	2.5	4	3.4
CHLORHEXIDINE GLUCONATE	1	0.8	0	0.0
CHLOROQUINE PHOSPHATE	0	0.0	1	0.8
CHLORPHENIRAMINE MALEATE	2	1.7	0	0.0
CHLORTHALIDONE	1	0.8	3	2.5
CHOLECALCIFEROL	4	3.3	2	1.7
CHOLESTYRAMINE	0	0.0	1	0.8
CIPROFLOXACIN	1	0.8	5	4.2
CITALOPRAM HCL	1	0.8	0	0.0
CITALOPRAM HYDROBROMIDE	6	5.0	7	5.9
CLARITHROMYCIN	2	1.7	2	1.7
CLINDAMYCIN HCL	3	2.5	0	0.0

CLONAZEPAM	0	0.0	1	0.8
CLONIDINE HCL	1	0.8	3	2.5
CLOPIDOGREL BISULFATE	1	0.8	4	3.4
COD LIVER OIL	0	0.0	1	0.8
CODEINE PHOS/ACETAMINOPHEN	7	5.8	6	5.1
CODEINE PHOS/ASPIRIN	0	0.0	1	0.8
COLCHICINE	2	1.7	1	0.8
CORTISONE ACETATE	2	1.7	2	1.7
CROMOLYN SODIUM	1	0.8	0	0.0
CYANOCOBALAMIN	1	0.8	1	0.8
CYCLOBENZAPRINE HCL	0	0.0	2	1.7
D-METHORPHAN HB/ACETAMINOPHEN	8	6.6	0	0.0
D-METHORPHAN HB/P-EPD HCL/APAP	0	0.0	2	1.7
D-METHORPHAN HB/P-EPD HCL/BPM	1	0.8	0	0.0
D-METHORPHAN HB/P-EPHED HCL	0	0.0	1	0.8
D-METHORPHAN HB/P-EPHED HCL/CP	0	0.0	1	0.8
D-METHORPHAN/P-EPHED/ACETAMINP	1	0.8	4	3.4
DALTEPARIN SODIUM,PORCINE	1	0.8	0	0.0
DESLORATADINE	2	1.7	5	4.2
DESMOPRESSIN (NONREFRIGERATED)	0	0.0	1	0.8
DESOGESTREL-ETHINYL ESTRADIOL	1	0.8	0	0.0
DESOXIMETASONE	0	0.0	1	0.8
DEXAMETHASONE	1	0.8	0	0.0
DEXTROMETHORPHAN	0	0.0	4	3.4
DEXTROMETHORPHAN HBR	1	0.8	0	0.0
DHCODEINE BT/ACETAMINOPHN/CAFF	0	0.0	1	0.8

DICLOFENAC SODIUM/MISOPROSTOL	0	0.0	3	2.5
DIETARY SUPPLEMENT	0	0.0	1	0.8
DIFLUNISAL	1	0.8	0	0.0
DIGOXIN	0	0.0	2	1.7
DILTIAZEM HCL	4	3.3	4	3.4
DIMENHYDRINATE	0	0.0	4	3.4
DIPHENHYDRAMINE CITRATE	1	0.8	3	2.5
DIPHENHYDRAMINE HCL	4	3.3	9	7.6
DIVALPROEX SODIUM	1	0.8	1	0.8
DL-ALPHA TOCOPHEROL	3	2.5	0	0.0
DL-ALPHA TOCOPHERYL ACETATE	0	0.0	1	0.8
DM HB/PSEUDOEPHED/ACETAMIN/CP	0	0.0	2	1.7
DOCOSAHEXANOIC ACID/EPA	4	3.3	0	0.0
DOCUSATE SODIUM	2	1.7	2	1.7
DOMPERIDONE	0	0.0	1	0.8
DOXAZOSIN MESYLATE	0	0.0	1	0.8
DOXYCYCLINE HYCLATE	0	0.0	1	0.8
DOXYCYCLINE MONOHYDRATE	0	0.0	3	2.5
DULOXETINE HCL	2	1.7	2	1.7
DUTASTERIDE	1	0.8	0	0.0
ECHINACEA	1	0.8	3	2.5
ECONAZOLE NITRATE	0	0.0	1	0.8
ENALAPRIL MALEATE	3	2.5	0	0.0
EPHEDRINE	0	0.0	1	0.8
ERYTHROMYCIN BASE	0	0.0	1	0.8
ESCITALOPRAM OXALATE	2	1.7	0	0.0

ESOMEPRAZOLE MAG TRIHYDRATE	4	3.3	10	8.5
ESTRADIOL	2	1.7	1	0.8
ESTRADIOL VALERATE	1	0.8	0	0.0
ESTROGEN,CON/M-PROGEST ACET	0	0.0	1	0.8
ESTROGENS,CONJ.,SYNTHETIC A	1	0.8	0	0.0
ESTROGENS,CONJUGATED	1	0.8	5	4.2
ESZOPICLONE	0	0.0	2	1.7
ETIDRONATE DISODIUM	1	0.8	0	0.0
ETODOLAC	2	1.7	1	0.8
EUCALYPT/MEN/CAMP/TURP/PET,WH	1	0.8	0	0.0
EXENATIDE	4	3.3	0	0.0
EZETIMIBE	2	1.7	9	7.6
EZETIMIBE/SIMVASTATIN	0	0.0	4	3.4
FA/MV,CA,FE,MIN/LYCOPENE/LUT	1	0.8	0	0.0
FAMOTIDINE	0	0.0	2	1.7
FELODIPINE	0	0.0	5	4.2
FENOFIBRATE NANOCRYSTALLIZED	2	1.7	1	0.8
FENOFIBRATE,MICRONIZED	1	0.8	2	1.7
FENTANYL	1	0.8	0	0.0
FERROUS FUMARATE	3	2.5	1	0.8
FERROUS SULFATE	3	2.5	1	0.8
FEXOFENADINE HCL	6	5.0	4	3.4
FINASTERIDE	2	1.7	0	0.0
FISH OIL/OMEGA-3 FATTY ACIDS	2	1.7	0	0.0
FLAXSEED OIL	1	0.8	1	0.8
FLUNISOLIDE	1	0.8	0	0.0

FLUOXETINE	3	2.5	1	0.8
FLUOXETINE HCL	3	2.5	6	5.1
FLUTICASONE FUROATE	1	0.8	0	0.0
FLUTICASONE PROPIONATE	6	5.0	11	9.3
FLUTICASONE/SALMETEROL	1	0.8	7	5.9
FLUVASTATIN SODIUM	1	0.8	0	0.0
FOLIC ACID	1	0.8	0	0.0
FOLIC ACID/MV,FE,OTHER MIN	1	0.8	0	0.0
FORMOTEROL FUMARATE	1	0.8	0	0.0
FOSINOPRIL SODIUM	1	0.8	0	0.0
FUROSEMIDE	1	0.8	5	4.2
GABAPENTIN	2	1.7	3	2.5
GARLIC	1	0.8	1	0.8
GEMFIBROZIL	1	0.8	1	0.8
GENTAMICIN IN SALINE, ISO-OSM	1	0.8	0	0.0
GENTAMICIN SULFATE	0	0.0	2	1.7
GENTAMICIN/SODIUM CHLORIDE	0	0.0	1	0.8
GINKGO BILOBA	0	0.0	1	0.8
GINSENG	0	0.0	3	2.5
GLIMEPIRIDE	0	0.0	1	0.8
GLIPIZIDE	2	1.7	3	2.5
GLIPIZIDE/METFORMIN HCL	1	0.8	0	0.0
GLUC HCL/CSA/COLL HY/HYALUR AC	2	1.7	1	0.8
GLUC SU/CHONDR SU A NA/SODIUM	1	0.8	1	0.8
GLUC SU/CHONDRO SU A/VIT C/MN	1	0.8	0	0.0
GLUC SU/CHONDROITIN SULFATE A	1	0.8	0	0.0

GLUCOSAMINE HCL	2	1.7	1	0.8
GLUCOSAMINE HCL/CHONDR SU A NA	1	0.8	0	0.0
GLUCOSAMINE SULFATE	1	0.8	1	0.8
GLYBURIDE	1	0.8	2	1.7
GUAIF/PSE/CODEINE/TRIPROLIDINE	1	0.8	0	0.0
GUAIFEN/PSEUDOEPHED/ACETAMINOP	2	1.7	2	1.7
GUAIFENESIN/D-METHORPHAN HB	0	0.0	3	2.5
GUAIFENESIN/P-EPHED HCL	0	0.0	1	0.8
GUAIFENESIN/PHENYLEPHRINE HCL	1	0.8	0	0.0
HC/MINERAL OIL/PETROLAT,WHT	1	0.8	0	0.0
HEP B VACCINE/HEP A VACCINE	0	0.0	2	1.7
HEPATITIS A & B VACCINE/PF	2	1.7	0	0.0
HERBAL DRUGS	14	11.6	3	2.5
HERBAL DRUGS/PUMPKIN SEED OIL	1	0.8	0	0.0
HUM INSULIN NPH/REG INSULIN HM	1	0.8	0	0.0
HYALURONATE SODIUM	0	0.0	1	0.8
HYDRALAZINE HCL	0	0.0	1	0.8
HYDROCHLOROTHIAZIDE	9	7.4	13	11.0
HYDROCODONE BIT/ACETAMINOPHEN	2	1.7	5	4.2
HYDROCODONE BIT/HOMATROPINE	1	0.8	5	4.2
HYDROCORTISONE	2	1.7	0	0.0
HYDROCORTISONE VALERATE	0	0.0	1	0.8
HYDROCORTISONE/ALOE VERA	0	0.0	1	0.8
HYDROGEN PEROXIDE	1	0.8	0	0.0
HYDROXYZINE HCL	0	0.0	1	0.8
HYOSCYAMINE SULFATE	1	0.8	0	0.0

HYPROMELLOSE/PF	1	0.8	0	0.0
IBANDRONATE SODIUM	1	0.8	0	0.0
IBUPROFEN	62	51.2	56	47.5
IBUPROFEN/P-EPHED HCL/CP	0	0.0	1	0.8
IBUPROFEN/PSEUDOEPHEDRINE HCL	5	4.1	8	6.8
IMIPRAMINE HCL	1	0.8	0	0.0
INDOMETHACIN	1	0.8	2	1.7
INFLUENZA TV-S 05-06 VACCINE	2	1.7	1	0.8
INSULIN DETEMIR	0	0.0	1	0.8
INSULIN GLARGINE,HUM.REC.ANLOG	0	0.0	3	2.5
INSULIN LISPRO,HUMAN REC.ANLOG	0	0.0	2	1.7
INSULIN NPH HUMAN RECOM	1	0.8	0	0.0
INSULIN NPL/INSULIN LISPRO	0	0.0	2	1.7
INSULIN REGULAR, HUMAN	0	0.0	2	1.7
IPRATROPIUM BROMIDE	1	0.8	1	0.8
IRBESARTAN	0	0.0	2	1.7
IRBESARTAN/HYDROCHLOROTHIAZIDE	0	0.0	1	0.8
IRON	1	0.8	1	0.8
KETOPROFEN	0	0.0	1	0.8
LABETALOL HCL	1	0.8	3	2.5
LAMOTRIGINE	2	1.7	0	0.0
LANCETS	0	0.0	1	0.8
LANSOPRAZOLE	1	0.8	1	0.8
LATANOPROST	2	1.7	1	0.8
LEVOFLOXACIN	3	2.5	2	1.7
LEVOTHYROXINE SODIUM	11	9.1	10	8.5

LIDOCAINE HCL	1	0.8	1	0.8
LISINOPRIL	11	9.1	5	4.2
LISINOPRIL/HYDROCHLOROTHIAZIDE	1	0.8	1	0.8
LITHIUM	0	0.0	1	0.8
LITHIUM CARBONATE	2	1.7	3	2.5
LOPERAMIDE HCL	1	0.8	6	5.1
LORATADINE	3	2.5	8	6.8
LORAZEPAM	1	0.8	1	0.8
LOSARTAN POTASSIUM	2	1.7	3	2.5
LOSARTAN/HYDROCHLOROTHIAZIDE	0	0.0	1	0.8
LOVASTATIN	1	0.8	0	0.0
LUBIPROSTONE	1	0.8	0	0.0
LUMIRACOXIB	0	0.0	1	0.8
MAG CARB/AL HYDROX/ALGINIC AC	1	0.8	0	0.0
MECLIZINE HCL	1	0.8	0	0.0
MEDROXYPROGESTERONE ACET	1	0.8	2	1.7
MELOXICAM	3	2.5	3	2.5
MENTHOL/CAMPHOR	0	0.0	1	0.8
MENTHOL/CETYLPYRD CL	0	0.0	1	0.8
MEPERIDINE HCL	1	0.8	0	0.0
METAXALONE	1	0.8	0	0.0
METFORMIN HCL	11	9.1	13	11.0
METHADONE HCL	1	0.8	1	0.8
METHOCARBAMOL	2	1.7	8	6.8
METHOCARBAMOL/ASPIRIN	3	2.5	0	0.0
METHYLPREDNISOLONE ACETATE	0	0.0	1	0.8

METOCLOPRAMIDE HCL	1	0.8	0	0.0
METOPROL/HYDROCHLOROTHIAZIDE	3	2.5	2	1.7
METOPROLOL SUCCINATE	4	3.3	1	0.8
METOPROLOL TARTRATE	2	1.7	3	2.5
METRONIDAZOLE	1	0.8	3	2.5
MIDAZOLAM	1	0.8	0	0.0
MILK THISTLE	1	0.8	0	0.0
MINERAL OIL	1	0.8	0	0.0
MIRTAZAPINE	1	0.8	3	2.5
MOMETASONE FUROATE	6	5.0	11	9.3
MONTELUKAST SODIUM	1	0.8	2	1.7
MORPHINE	1	0.8	0	0.0
MORPHINE SULFATE	0	0.0	2	1.7
MOXIFLOXACIN HCL	3	2.5	2	1.7
MULTIVITAMINS	16	13.2	11	9.3
MULTIVITAMINS W-MINERALS	3	2.5	2	1.7
MULTIVITAMINS W-MINERALS/LUT	1	0.8	1	0.8
MULTIVITS,TH W-CA,FE,OTH MIN	0	0.0	1	0.8
MULTIVITS,THERAP W-FE,HEMATIN	1	0.8	0	0.0
MUPIROCIN CALCIUM	0	0.0	1	0.8
NABUMETONE	1	0.8	1	0.8
NAPHAZOLINE HCL/ANTAZOLINE	0	0.0	1	0.8
NAPROXEN	2	1.7	5	4.2
NAPROXEN SODIUM	7	5.8	3	2.5
NAPROXEN SODIUM/P-EPHED HCL	0	0.0	1	0.8
NATEGLINIDE	0	0.0	1	0.8

NEOMY SULF/BACITRAC ZN/POLY	3	2.5	0	0.0
NEOMYCIN/BACITRA/POLYMYXIN/HC	0	0.0	1	0.8
NIACIN	5	4.1	2	1.7
NIFEDIPINE	4	3.3	1	0.8
NITROFURANTOIN	1	0.8	0	0.0
NITROGLYCERIN	4	3.3	6	5.1
NORETH A-ET ESTRA/FE FUMARATE	2	1.7	0	0.0
NORETHINDRONE	1	0.8	0	0.0
NORFLOXACIN	0	0.0	1	0.8
NORGESTIMATE-ETHINYL ESTRADIOL	1	0.8	0	0.0
NORMAL SALINE	0	0.0	1	0.8
NPH, HUMAN INSULIN ISOPHANE	0	0.0	2	1.7
NYSTATIN/TRIAMCIN	0	0.0	1	0.8
OLMESARTAN MEDOXOMIL	0	0.0	1	0.8
OLOPATADINE HCL	0	0.0	2	1.7
OMEGA-3 FATTY ACIDS	4	3.3	4	3.4
OMEPRAZOLE	5	4.1	7	5.9
OMEPRAZOLE MAGNESIUM	1	0.8	0	0.0
ORLISTAT	1	0.8	0	0.0
OXAZEPAM	1	0.8	0	0.0
OXYCODONE HCL	1	0.8	3	2.5
OXYCODONE HCL/ACETAMINOPHEN	4	3.3	3	2.5
P-EPHED HCL/ACETAMINOPHEN	1	0.8	1	0.8
P-EPHED HCL/ACETAMINOPHN/CP	0	0.0	1	0.8
P-EPHED HCL/ACETAMINOPHN/DPHA	0	0.0	2	1.7
P-EPHED HCL/TRIPROLIDINE HCL	2	1.7	1	0.8

P-EPHED SUL/LORATADINE	0	0.0	3	2.5
PAMIDRONATE DISODIUM	0	0.0	1	0.8
PANTOPRAZOLE SODIUM	1	0.8	1	0.8
PARICALCITOL	1	0.8	0	0.0
PAROXETINE HCL	14	11.6	6	5.1
PE/HYDROCODONE/DEXBROMPHENIRMN	1	0.8	0	0.0
PEN G POT/DEXTROSE-WATER	0	0.0	1	0.8
PENICILLIN V	0	0.0	2	1.7
PENICILLIN V POTASSIUM	0	0.0	2	1.7
PERINDOPRIL ERBUMINE	1	0.8	0	0.0
PHENIRAMINE MALEATE	0	0.0	1	0.8
PHENYLEPHRINE HCL	1	0.8	3	2.5
PHENYLEPHRINE/CHLOR-MAL/SCOP	1	0.8	0	0.0
PHENYTOIN	1	0.8	1	0.8
PIOGLITAZONE HCL	0	0.0	5	4.2
POTASSIUM	1	0.8	0	0.0
POTASSIUM CHLORIDE	0	0.0	3	2.5
POTASSIUM PHOS,M-BASIC-D-BASIC	1	0.8	0	0.0
PRAVASTATIN SODIUM	1	0.8	1	0.8
PREDNISONE	4	3.3	9	7.6
PROGESTERONE	0	0.0	1	0.8
PROMETHAZINE HCL	1	0.8	0	0.0
PROPAFENONE HCL	0	0.0	1	0.8
PROPOXYPHENE/ACETAMINOPHEN	1	0.8	0	0.0
PROPRANOLOL HCL	2	1.7	0	0.0
PROPYLENE GLYCOL/PEG'S	0	0.0	1	0.8

PSEUDOEPHEDRINE HCL	0	0.0	5	4.2
PYRIDOXINE HCL	1	0.8	0	0.0
QUETIAPINE FUMARATE	0	0.0	3	2.5
QUINAPRIL HCL	0	0.0	1	0.8
QUINAPRIL/HYDROCHLOROTHIAZIDE	1	0.8	0	0.0
QUININE SULFATE	0	0.0	1	0.8
RABEPRAZOLE SODIUM	2	1.7	3	2.5
RAMIPRIL	2	1.7	5	4.2
RANITIDINE HCL	5	4.1	1	0.8
RED YEAST RICE EXTRACT	1	0.8	0	0.0
REPAGLINIDE	0	0.0	1	0.8
RIFABUTIN	0	0.0	1	0.8
RISEDRONATE SODIUM	0	0.0	2	1.7
RISPERIDONE	1	0.8	0	0.0
ROFECOXIB	1	0.8	0	0.0
ROPINIROLE HCL	1	0.8	0	0.0
ROSIGLITAZONE MALEATE	2	1.7	2	1.7
ROSIGLITAZONE/METFORMIN HCL	0	0.0	1	0.8
ROSUVASTATIN CALCIUM	7	5.8	2	1.7
SALM OIL/VIT E MIX/SOY/FAT 3	0	0.0	1	0.8
SALMETEROL XINAFOATE	0	0.0	1	0.8
SAW PALMETTO	2	1.7	0	0.0
SERTRALINE HCL	5	4.1	5	4.2
SILDENAFIL CITRATE	0	0.0	2	1.7
SIMVASTATIN	6	5.0	5	4.2
SITAGLIPTIN PHOSPHATE	0	0.0	2	1.7

SODIUM CHLORIDE	1	0.8	1	0.8
SPIRONOLACTONE	0	0.0	1	0.8
SULFAMETHOXAZOLE/TRIMETHOPRIM	1	0.8	0	0.0
SUMATRIPTAN	2	1.7	0	0.0
TADALAFIL	0	0.0	1	0.8
TAMSULOSIN HCL	1	0.8	2	1.7
TEGASEROD HYDROGEN MALEATE	0	0.0	2	1.7
TELMISARTAN	3	2.5	2	1.7
ZOLPIDEM TARTRATE	1	0.8	6	5.1
TELMISARTAN/HYDROCHLOROTHIAZID	1	0.8	0	0.0
TERBUTALINE SULFATE	0	0.0	2	1.7
TESTOSTERONE	2	1.7	1	0.8
TETRACYCLINE	1	0.8	0	0.0
TETRAHYDROZOLINE HCL	0	0.0	1	0.8
TIMOLOL MALEATE	2	1.7	0	0.0
TIOTROPIUM BROMIDE	1	0.8	2	1.7
TOPIRAMATE	1	0.8	1	0.8
TORSEMIDE	1	0.8	0	0.0
TRAMADOL HCL	1	0.8	3	2.5
TRAVOPROST	0	0.0	1	0.8
TRAZODONE HCL	2	1.7	5	4.2
TRIAMCINOLONE ACETONIDE	2	1.7	6	5.1
TRIAMTERENE	0	0.0	2	1.7
TRIAMTERENE/HYDROCHLOROTHIAZID	4	3.3	1	0.8
TRIAZOLAM	0	0.0	1	0.8
TRIHEXYPHENIDYL HCL	1	0.8	0	0.0

UBIDECARENONE	3	2.5	0	0.0
VALACYCLOVIR HCL	3	2.5	0	0.0
VALPROIC ACID	0	0.0	1	0.8
VALSARTAN	6	5.0	1	0.8
VALSARTAN/HYDROCHLOROTHIAZIDE	2	1.7	2	1.7
VENLAFAXINE HCL	5	4.1	4	3.4
VITAMIN B COMPLEX	3	2.5	3	2.5
VITAMIN C	2	1.7	0	0.0
VITAMIN E	1	0.8	0	0.0
WARFARIN SODIUM	1	0.8	4	3.4
XYLOMETAZOLINE HCL	2	1.7	0	0.0
ZINC	1	0.8	0	0.0
ZINC GLUCONATE	0	0.0	1	0.8
ZOPICLONE	4	3.3	0	0.0

SUPPLEMENTARY TABLE E5. BASELINE PARTICIPANT CHARACTERISTICS OF THOSE RANDOMIZED BUT NOT EXPOSED TO CPAP

Variable	N	% or Mean ± Standard Deviation	Median
Percent males	42	60%	
Percent African Americans	42	26.19%	
Percent married	42	52.38%	
Percent high school education	42	23.81%	
Percent work full time	42	64.29%	
Age (years)	42	48.76 ± 12.93	47
FOSQ Total Score	25	15.21 ± 1.88	15.44
ESS Score	25	15.48 ± 4.24	17

SUPPLEMENTARY TABLE E6. EFFICACY CHANGE OF SECONDARY SUBJECTIVE OUTCOMES FROM PRE-TREATMENT BASELINE TO THE END OF THE INITIAL 8-WEEK TREATMENT PERIOD[1] IN THE MODIFIED INTENT TO TREAT SAMPLE[2]

Endpoint	Active Adjusted Mean Change[2]	Sham Adjusted Mean Change[2]	Adjusted Difference in Mean Change[2]	SE	p Value[3]	95% CI for Difference in Mean Changes	
						Lower Bound	Upper Bound
SF-36							
Physical Component	3.89	.04	3.85	1.17	.001	1.53	6.17
Mental Health Component	3.07	2.21	.86	1.42	.546	-1.95	3.67
Physical Functioning	8.97	1.83	7.14	2.35	.003	2.49	11.79
RP Role Physical	11.41	2.05	9.36	5.95	.118	-2.40	21.12
Bodily Pain	9.25	1.13	8.12	2.69	.003	2.81	13.44
General Health	6.27	-.35	6.61	2.42	.007	1.82	11.41
Vitality	12.66	6.07	6.59	3.14	.037	.39	12.80

Social Functioning	7.15	2.95	4.20	2.72	.125	-1.19	9.59
Role Emotional	8.68	7.39	1.29	6.10	.833	-10.77	13.35
Mental Health	4.80	2.27	2.54	2.12	.234	-1.66	6.73
ESS	-2.46	-.68	-1.78	.52	.001	-2.82	-.75
POMS							
Fatigue Score	-2.7	-.5	-2.27	.83	.007	-3.9	-.6
Confusion-Bewilderment	-1.5	-.4	-1.09	.42	.011	-1.9	-.3
Tension-Anxiety Score	-.5	-.8	.30	.52	.565	-.7	1.3
Vigor Score	2.8	-.1	2.89	.75	0	1.4	4.4
Depression-Dejection	-.8	-.4	-.37	.79	.640	-1.9	1.2
Anger-Hostility	-.3	.1	-.35	.62	.574	-1.6	.9
Total Mood Disturbance	-8.9	-1.7	-7.22	2.91	.014	-13	-1.5

Notes:

1 Adjusted mean changes and adjusted differences in mean changes were estimated as site-total-sample-size weighted values controlling for treatment group differences in mean pre treatment baseline values.

[2] The Intent-to-Treat sample includes all randomized patients exposed to active CPAP or sham-CPAP treatment during the post randomization treatment.

[3] P-value from Type II sum of squares estimated by way of analysis of covariance. To produce site weighted comparisons the ANCOVA model included main effects for treatment group, site, and pre-treatment baseline value.

SUPPLEMENTARY TABLE E7. EFFICACY CHANGE OF SECONDARY OBJECTIVE OUTCOMES FROM PRE-TREATMENT BASELINE TO THE END OF THE INITIAL 8-WEEK TREATMENT PERIOD[1] IN THE MODIFIED INTENT TO TREAT SAMPLE[2]

Endpoint	Active Adjusted Mean Change[2]	Sham Adjusted Mean Change[2]	Adjusted Difference in Mean Change[2]	SE	P Value[3]	Lower and Upper Bounds of 95% CI for Difference in Mean Changes	
Psychomotor Vigilance Task							
Lapses/Trial	-2.00	2.33	-4.33	2.78	.121	-9.80	1.15
Median RT (ms)	-13.25	9.86	-23.12	12.93	.0075	-48.62	2.39
Fastest 10% RT (ms)	-4.93	-.26	-4.68	4.36	.285	-13.29	3.93
Slowest 10% 1/RT	.07	-.15	.22	.07	.002	.08	.36
Mood VAS	-1.28	-.17	-1.11	.31	0	-1.73	-.50
Ambulatory 48-hr blood pressure							
Heart rate - day	-0.62	0.20	-0.82	1.10	0.457	-3.0	1.4
Systolic BP - day	0.72	2.04	-1.32	1.58	0.407	-4.5	1.8
Diastolic BP - day	-0.57	1.36	-1.93	0.96	0.048	-3.8	0.0
MAP - day	-0.59	1.17	-1.76	1.03	0.090	-3.8	0.3

Heart rate - night	-0.61	0.03	-0.64	1.01	0.530	-2.6	1.4
Systolic BP - night	-0.10	2.10	-2.21	1.86	0.239	-5.9	1.5
Diastolic BP - night	-0.31	1.21	-1.51	1.23	0.222	-4.0	0.9
MAP – night	-0.60	1.61	-1.77	1.34	0.190	-4.4	0.9
Heart rate - dip	0.10	0.50	-0.40	1.02	0.694	-2.4	1.6
Systolic - dip	-0.46	-0.66	0.20	1.36	0.885	-2.5	2.9
Diastolic - dip	0.49	-0.18	0.66	1.04	0.526	-1.4	2.7
MAP - dip	0.30	-0.49	0.79	1.10	0.474	-1.4	3.0

Notes:

1 Adjusted mean changes and adjusted differences in mean changes were estimated as site-total-sample-size weighted values controlling for treatment group differences in mean pre treatment baseline values.

[2] The Intent-to-Treat sample includes all randomized patients exposed to active CPAP or sham-CPAP treatment during the post randomization treatment.

[3] P-value from Type II sum of squares estimated by way of analysis of covariance. To produce site weighted comparisons the ANCOVA model included main effects for treatment group, site, and pre-treatment baseline value.

SUPPLEMENTARY TABLE E8. PARTICIPANT CHARACTERISTICS OF THE CROSS-OVER COHORT (N=99) JUST PRIOR TO BEGINNING ACTIVE CPAP INTERVENTION, I.E., AT THE 8-WEEK SHAM CPAP FOLLOW-UP ASSESSMENT.

Variable	
Age (years)	49.3 ± 11.1
Percent males	61.8
Percent African Americans	15.7
Body mass index (kg/m^2)	33.3 ± 6.6
Weight (lbs.)	213.8 ± 209.5
FOSQ Total score	14.24 ± 2.75
General productivity	2.99 ± 0.61
Vigilance	2.56 ± 0.64
Social outcome	3.03 ± 0.69
Activity level	2.65 ± 0.64
Intimacy & sexual relationships	3.03 ± 0.98

SUPPLEMENTARY TABLE E9. MEAN CHANGE IN FOSQ TOTAL AND COMPONENT SCORES IN THE CROSS-OVER.

Endpoint	n	Mean ± SD	Min	Max	Effect size	p-value
FOSQ						
Total Score	91	1.73 ± 2.50	-6.95	9.43	0.690	< 0.001
General Productivity	91	0.27 ± 0.52	-0.95	1.86	0.514	< 0.001
Vigilance	90	0.40 ± 0.66	-2.00	2.29	0.613	< 0.001
Social Outcome	88	0.34 ± 0.73	-2.50	3.00	0.465	< 0.001
Activity Level	91	0.38 ± 0.56	-1.25	2.11	0.681	< 0.001
Intimacy & Sexual Relationships	75	0.30 ± 0.66	-1.00	2.50	0.462	< 0.001
ESS	92	-2.29 ± 3.99	-13.0	7.00	-0.575	< 0.001
PVT						
Lapses/trial	80	-3.93 ± 13.46	-70.5	27.0	-0.292	0.0108
PVT Median RT	80	-17.2 ± 46.1	-284.0	75.50	-0.374	0.0012
PVT Fast 10% RT	80	-7.0 ± 17.2	-65.4	44.4	-0.409	0.0005
PVT Slowest 10% 1/RT	80	0.18 ± 0.57	-1.44	1.90	0.323	0.0050
Fatigue score	97	-2.4 ± 6.6	-18.0	14.0	-0.366	0.0005
POMS						
Confusion-bewilderment	97	-1.1 ± 3.2	-9.0	10.0	-0.354	0.0008
Tension-anxiety score	97	-0.1 ± 4.7	-14.0	20.0	-0.023	0.8218

Vigor score	97	3.1 ± 5.6	-16.0	17.0	0.555	0.0000
Depression-dejection	97	-0.7 ± 6.6	-23.6	34.0	-0.101	0.3228
Anger-hostility	97	0.0 ± 4.2	-16.4	12.0	0.008	0.9347
Total mood disturbance	97	-7.4 ± 23.5	-63.0	86.0	-0.314	0.0026
SF36						
Physical Component	62	2.50 ± 7.70	-15.87	26.31	0.324	0.0132
Mental Health Component	62	3.40 ± 8.38	-25.02	29.21	0.406	0.0022
Ambulatory Blood Pressure						
Systolic BP - Day	46	1.80 ± 7.92	-14.67	29.61	0.227	0.1311
Diastolic BP - Day	46	0.21 ± 5.13	-13.13	12.13	0.041	0.7827
MAP - Day	46	0.64 ± 5.21	-12.79	14.73	0.124	0.4060
Systolic BP - Night	46	-1.54 ± 8.99	-17.85	15.48	-0.171	0.2509
Diastolic BP - Night	46	-1.61 ± 5.91	-17.57	11.66	-0.272	0.0712
MAP - Night	46	-1.23 ± 6.36	-15.15	10.48	-0.193	0.1971
Systolic BP - Dip	44	-3.00 ± 9.94	-34.34	12.91	-0.302	0.0518
Diastolic BP - Dip	44	-1.63 ± 6.30	-16.45	11.14	-0.259	0.0935
MAP - Dip	44	-1.71 ± 6.78	-17.46	12.04	-0.252	0.1018