CPAP and Cognition in OSA (APPLES)

Commentary on Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *SLEEP* 2012;35:1593-1602.

David J. Berlowitz, Ph.D.¹; Shirin Shafazand, M.D., M.S., F.A.A.S.M.²

¹Institute for Breathing and Sleep, Melbourne, Australia; ²University of Miami, Miami, Florida

ARTICLE SUMMARY

Question: What is the effect of continuous positive airway pressure (CPAP) therapy versus Sham CPAP therapy on neurocognitive function in patients with obstructive sleep apnea (OSA)?

Design: Multi-center, randomized, double blinded, sham controlled trial; ClinicalTrials.gov Identifier: NCT00051363.

Allocation: The Data Coordinating Center used a computerized permuted block design to randomize participants to the 2 study arms.

Blinding: Participants and most personnel were blinded to treatment assignments, with the exception of site coordinators, polysomnography (PSG) technologists, and the database administrator/data manager.

Follow-up period: 6 month follow-up; the first participant was enrolled in 11/2003 and the final completion month was 8/2008.

Setting: 5 clinical sleep centers in the United States (academic and private settings).

Subjects: 1,098 participants (556 active CPAP, 542 sham CPAP, 35% women, mean age 52 years in active CPAP group) who were diagnosed with OSA with apnea hypopnea index (AHI) ≥ 10 events per hour were randomized. The primary exclusion criteria were: 1) prior OSA treatment with CPAP or surgery; 2) anyone in the household with current/past CPAP use; 3) sleepiness-related automobile accident within past year; 4) oxygen saturation $< 75\%$ for $> 10\%$ of the diagnostic PSG total sleep time; and/or 5) conditions (including known neurocognitive impairment), disorders, medications, or substances that could potentially affect neurocognitive function and/or alertness. Subjects were recruited primarily from patients scheduled in a regular sleep clinic for evaluation of possible OSA and from local advertising. Although recruitment source was not tracked, it was estimated that initial contact with $\sim 70\%$ of the subjects occurred as a result of advertisement.

Intervention: Participants were randomized to receive CPAP treatment or sham CPAP. Outcomes: The primary outcomes were 3 neurocognitive variables, each representing a neurocognitive domain: 1) Pathfinder Number Test-Total Time assesses attention and psychomotor function; 2) Buschke Selective Reminding Test-Sum Recall assesses verbal learning and memory; and 3) Sustained Working Memory Test-Overall Mid-Day Index assesses an executive and frontal-lobe function

(E/F). The secondary outcomes were 7 neurocognitive and 2 sleepiness measures (the maintenance of wakefulness test and the Epworth Sleepiness Scale).

The sample size was based on pilot study results for the Pathfinder Number Test. A target of 1,100 total participants (assuming 90% power, 2-sided $\alpha = 0.05$, 20% study dropout, and allowing for 3 interim analyses) was estimated to achieve an effect size of 0.2, translating to the clinically significant difference of 26 msec in reaction time between the Active and Sham CPAP groups. An effect size of ≥ 0.2 is also a clinically significant between group difference for the other two primary outcome measures.

Patient Follow-Up: intention to treat analysis, 79% completed follow-up in active arm, 74% in sham arm.

Main Results: There was no statistically significant difference between the groups in the primary outcomes at 6 months. When stratified by measures of OSA severity (AHI or oxygen saturation parameters), the primary E/F variable and one secondary E/F neurocognitive variable revealed transient differences between study arms for those with the most severe OSA that did not persist at 6 months. When primary neurocognitive analyses were restricted to CPAP-adherent individuals (mean nightly active or sham CPAP adherence ≥ 4 h for the 2 months prior to each neurocognitive testing visit), no differences in means were detected between arms for any of the primary outcomes at any visit.

Participants in the active CPAP group had a significantly greater ability to remain awake whether measured subjectively by the Epworth Sleepiness Scale or objectively by the maintenance of wakefulness test.

Conclusion: In adults with OSA, CPAP therapy did not improve neurocognitive measures at 6 months compared with those on sham CPAP therapy.

Sources of Funding: APPLES was funded by NHLBI (HL68080). The APPLES pilot studies were supported by grants from the American Academy of Sleep Medicine and the Sleep Medicine Education and Research Foundation to Stanford University and by the NINDS (N44NS002394) to SAM Technology. Respiroics®, Inc. supplied the active- and sham-CPAP devices and equipment.

For Correspondence: Clete A. Kushida, M.D., Ph.D., F.A.A.S.M.; Email: clea@stanford.edu

COMMENTARY

The effect of Continuous Positive Airway Pressure (CPAP) treatment for Obstructive Sleep Apnea (OSA) on neurocognitive function (APPLES) is an NIH-funded, impeccably designed and executed RCT from experts in the field which is essentially a negative study. The primary aim of this five year, multi-site investigation was to determine, with sufficient statistical power, whether neurocognitive function is improved by CPAP treatment for OSA.

From the point of view of the primary endpoints, the finding of a small deterioration in the Sham condition at 2 months, in the domain of frontal lobe and executive function (E/F), rather than any large improvement in the Active arm is intriguing. There remains a chance that it was a type 1 statistical error. However this seems unlikely because as the authors delved deeper into the efficacy analysis, the difference in outcomes favoring Active at 2-months appeared to strengthen overall, particularly in participants with more severe OSA and sleep dysfunction at baseline. One might speculate that the improvements in sleepiness seen in those adherent with therapy were mediating the lack of deterioration in E/F and furthermore that these benefits were less able to be built upon from 2 to 6 months (as the sleepiness was already “cured”). As the authors note, perhaps the study sample was fundamentally biased towards those with more cognitive reserve and thus the potential for improvement with treatment reduced. Additionally, the greater reduction in adherence observed in the Sham group, and the subsequent loss of statistical power of the efficacy analyses, may also reignite the debate as to what is an appropriate Sham for CPAP; sugar pills are well tolerated (93% adherence) and preferred by participants over CPAP.¹ Regardless, the data support the authors’ conclusion that the relationship between OSA and neurocognition, particularly in more severe disease, is real and complex.

The authors and the journal are also to be commended for the publication of the results contained in the Appendices. These comprehensive data substantially increase the information available to the scientific community from the study. I would attest that had an APPLES a day been found to substantially increase neurocognitive function, rather than the equivocal, arguably negative overall effect that was demonstrated, the paper would have been far shorter, published in a higher impact general medical journal and these valuable data would have struggled to see the light of day.² Negative studies are vital contributors to the body of knowledge about how and why CPAP works in OSA.

CITATION

Berlowitz DJ; Shafazand S. CPAP and cognition in OSA (APPLES). *J Clin Sleep Med* 2013;9(5):515-516.

REFERENCES

1. Barnes M, Houston D, Worsnop CJ, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;165:773-80.
2. Easterbrook PJ, Gopalan R, Berlin JA, Matthews DR. Publication bias in clinical research. *The Lancet* 1991;337:867-72.

CORRESPONDENCE INFORMATION

Address correspondence to: Shirin Shafazand, M.D., M.S., University of Miami, Division of Pulmonary, Critical Care and Sleep Medicine, PO Box 016960 (D60), Miami, FL, 33101, United States; Tel: (305) 243-7838; E-mail: sshafazand@med.miami.edu

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.