

The Influence of CPAP on the Neurobehavioral Performance of Patients with Obstructive Sleep Apnea Hypopnea Syndrome: A Systematic Review

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ABSTRACT

Objective: To determine what is known about neurobehavioral outcomes in patients with the obstructive sleep apnea hypopnea syndrome following treatment with continuous positive airway pressure (CPAP).

Data Sources: Medline was searched. Abstracts presented at international meetings were searched and authors were contacted for additional trials. Bibliographies of the retrieved articles were reviewed.

Study Selection: We reviewed all prospective studies that included: 1) a target population with obstructive sleep apnea, 2) CPAP as a study intervention, 3) evidence that the CPAP level was titrated until the AHI was <5, and 4) standardized neurobehavioral outcomes appropriate for assessing sleep apnea.

Data Synthesis: Twenty-six studies contributed to this qualitative systematic review. Effect sizes were calculated and adjusted for small samples and multiple measurements. Studies were then scored according to the outcome of the study.

Conclusions: This qualitative systematic review supports the assertion that CPAP has a significant and positive impact on subjective sleepiness and depression when randomized controlled trials are considered, and on fatigue, generic health-related quality of life, vigilance, and driving performance when all prospective trials are considered. These parameters appear to be sensitive to treatment duration and compliance. These

results should be considered when developing health policy and designing future clinical trials.

INTRODUCTION

The prevalence of the obstructive sleep apnea hypopnea syndrome (OSAHS), when defined as at least 5 apneas and hypopneas per hour of sleep accompanied by excessive daytime sleepiness, was 4% for males and 2% for females in a population of working adults 30 to 60 years of age.¹ Perhaps more interesting is the finding that less than 10% of those who met the criteria for OSAHS sought medical attention.² This would suggest that the majority of those with symptomatic OSAHS are currently undiagnosed. Defining the benefits of OSAHS treatment is of great interest to clinicians, researchers, health care agencies, and policy makers because of the magnitude of the population at risk.

The American Thoracic Society and American Sleep Disorders Association (ATS/ASDA) statement dealing with health outcomes research in sleep apnea³ identified neurobehavioral outcomes following continuous positive airway pressure (CPAP) therapy as an area that needed further evaluation. Neurobehavioral outcomes were defined as those that evaluated quality of life, general performance (psychomotor and cognitive function), neuropsychological assessment, and sleepiness. The therapeutic options for the management of OSAHS include weight loss,^{4,5} CPAP,⁶⁻⁹ bilevel positive airway pressure,^{10,11} mechanical advancement devices,^{12,13} and surgical procedures.¹⁴ Of these, nasal CPAP is most frequently used to treat OSAHS but its efficacy may be impaired by a low compliance rate.¹⁵⁻¹⁹

We performed a systematic review of prospective studies to investigate what is known about the neurobehavioral outcomes of patients with OSAHS following treatment with CPAP. The current study ex-

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plores the published data and includes 26 prospective studies.

METHODS

The target population consisted of subjects with a diagnosis of obstructive sleep apnea defined as an Apnea-Hypopnea Index (AHI) >5 events per hour. The study intervention included CPAP—there needed to be evidence that the CPAP was titrated until the AHI was <5. Outcomes of interest were consistent with the neurobehavioral classification described by the ATS/ASDA³ and included quality of life, psychomotor and cognitive function, neuropsychological assessment and subjective sleepiness assessment. All prospective studies, except case reports, were included.

Greater than 5 to 10 episodes of apnea or hypopnea per hour of sleep are considered beyond the broad limits of normal.²⁰ CPAP treatment was defined as positive airway pressure delivered through a nasal mask, nasal prongs, or a full-face mask.

Literature Search

We used several complementary search strategies to retrieve potentially relevant articles. First, we conducted a MEDLINE search through June 1999. Three searches were conducted: 1) the target population (sleep apnea syndromes, sleep apnea, sleep apnoea, osa) was combined with (using an “and”) the target intervention (positive-pressure respiration, cpap, CPAP, positive airway pressure, positive airways pressure); 2) the target outcomes (cognition, affect, activities of daily living, quality of life, neuropsychological tests, depression, affective disorders, fatigue, hypersomnia) were combined with (using an “and”) the target intervention; and finally 3) the results of the first search were combined with the second search (using an “or”). All terms were explored and were limited to studies with English language abstracts and human adults (>18 years old). We also reviewed the reference lists of relevant articles, guidelines of the ATS⁹ and the ASDA,²¹ and abstracts presented at national meetings to retrieve potentially relevant articles. Experts in the field were consulted about missing studies.

Article Selection

Subjects with central sleep apnea, Cheyne Stokes respiration, upper airways resistance syndrome, or obstructive sleep apnea as a consequence of neuromuscular, cardiac, or renal disease were excluded from this review. Treatment with bilevel positive airway pressure was excluded. Physiologic measures of sleepiness such as the multiple sleep latency test and the maintenance of wakefulness test were also excluded.

Appropriate articles for inclusion were chosen in a three-phase process. In phase 1, two reviewers (BHF and JPM) independently reviewed abstracts retrieved by the MEDLINE search to determine which articles were potentially appropriate for this review. Any article for which the title or abstract suggested any possibility that it might be relevant was photocopied. In phase 2, three reviewers (RCC, BHF, and JPM) independently reviewed the methods section of the articles retrieved in phase 1. The article was retained if all three reviewers independently felt that it satisfied the study criteria. Articles for which independent agreement was not reached were reviewed in detail, and unanimous consensus among the three reviewers was required for an article to be included at this point. In phase 3, the entire article was reviewed to extract data on study type, number of participants, controls used, outcome measure (based on the intent of the author), and outcome results to calculate the effect size. If complete outcome data for a variable could not be extracted, that data was excluded from the analysis. A log of the citations retrieved from the initial search and the reason for exclusion was maintained.

Data Extraction and Synthesis

A qualitative assessment of patient population, study design, treatment duration, and neurobehavioral outcome was performed. Disagreement was resolved by consensus.

Neurobehavioral test classification was based on the ATS/ASDA statement on health outcomes in sleep apnea research and included the categories sleepiness, quality of life, psychomotor and cognitive function, and neuropsychological assessments.³ In the ATS/ASDA statement paper, psychomotor and cognitive function tests include reaction time tests, vigilance tests, driving performance, finger tapping, and list recall, and neuropsychological assessments include standardized instruments to assess mood, anxiety, depression, memory, learning, and integrative functions. This classification system posed a problem because learning and integrative function appeared to overlap into both categories. Therefore, for this review, learning and integrative functions were considered part of psychomotor and cognitive function, which was renamed “Performance Assessment,” and the category neuropsychological was renamed “Psychological Assessment.”

We calculated an effect size for each neurobehavioral outcome for which complete assessment was possible. Due to the small sample sizes and multiple measurements in the majority of the studies, we represented the

Table 1. Summary of the article selection protocol

Phase	Total	Studies, n	
		Excluded*	Included
Phase 1: Title and Abstract Review	936	871	65
Did not include OSAHS	221		
Did not include CPAP	180		
Outcome was not Neurobehavioral		217	
Case Report, Letter, Editorial		110	
Other		143	
Phase 2: Methods and Results Review	65	37	28
OSA determination not provided		10	
CPAP titration not performed		11	
Neurobehavioral instrument not described		14	
Outcome measurements fail to meet criteria	22		
Phase 3: Detailed Review	28	2	26
Data previously published		1	
Insufficient data to calculate an effect size		1	

* Articles were excluded on more than one criterion.

effect size as “+” (a statistically significant difference favoring the treatment group), “0” (no significant difference), or “-” (a statistically significant difference favoring the control group).²² The entire study was then classified based on the overall number of individual assessments it contained as either: 1) supporting statistical improvement (+ >0); 2) failing to detect a statistical improvement (+ <0); or 3) producing no conclusion.

RESULTS

Literature Search

Nine hundred twenty-six articles were retrieved from the computerized search. Ten additional articles were retrieved following review of the references of relevant articles (n=9) and review of scientific meeting abstracts (n=1). Table 1 provides a summary of the article selection process.

Following the phase 1 screening process, 65 abstracts were identified as meeting the phase 1 inclusion criteria. The 871 abstracts were excluded for the following reasons: the study population did not have OSAHS (n=221); the study intervention did not in-

clude CPAP (n=180); the study outcome was other than neurobehavioral (compliance n=32, physiological n=112, technical n=45, biochemical n=28); the article was a case report, letter, or editorial (n=110); or other (n=143). Articles may have been rejected for more than one reason.

Sixty-five articles were evaluated during phase 2, and 28 articles were identified as meeting inclusion criteria. Articles were excluded for the following reason(s): OSAHS was not defined by either an AHI, respiratory disturbance index (RDI) or apnea index (AI) >5 (n=10); CPAP titration was not used to determine the optimal level of CPAP required to “normalize” the AHI/RDI/AI (n=11); the instrument used to measure the neurobehavioral outcome was not described (n=14); or the neurobehavioral state was not measured prior to and following CPAP therapy (n=22).

Twenty-eight articles were evaluated during phase 3, and 2 articles were rejected for the following reasons: the manuscript did not contain new data that had not been previously published elsewhere (n=1), and it was not possible to calculate the effect size from the data provided in the article (n=1). Therefore, 26 separate trials were finally considered in the review.

Study Characteristics

Table 2 summarizes study characteristics included in this systematic review. All studies were prospective, and the majority used a single cohort design in which the neurobehavioral outcome was measured in the same cohort before and after CPAP intervention. Four studies utilized a parallel cohort design. Of these, 3 studies used a comparison cohort with OSAHS who were not treated with CPAP, and a fourth study used a comparison cohort without OSAHS. Four studies used a single cohort in which either a placebo or CPAP was applied and afterward the alternative therapy was evaluated. In these studies the sequence of the interventions was randomized. Finally, 3 studies utilized a randomized control design with 1 using nasal strips, 1 with weight loss combined with improved sleep hygiene, and 1 used sub therapeutic CPAP.

Male patients accounted for approximately 85% of the combined study population. The CPAP duration across the studies had a range of 1 night to 1 year with a mean (SD) of 4.9 (4.1) months. The neurobehavioral outcomes most often measured were performance assessment and psychological assessment.

Performance Assessment

Nineteen studies evaluated performance assessment. They measured 14 different parameters of performance

Table 2. Studies included in the systematic review

Author (year)	Reference Number	Study Design	Subjects (% Male)	Comparison Group	AHI Mean (SD)	CPAP Duration Months (SD)	Neurobehavioral Outcome
Derderian (88)	23	Parallel Cohort	7 (100)	Untreated SAHS	40.7 (5.5)	2	Psy
Findley (89)	24	Single Cohort	6 (83)	Self Pre-treatment	83 (20)	3.5	Per
Ramos (92)	25	Single Cohort	5 and 23 (97)	Self Pre-treatment	61.1 (21.8)	11	Psy
Bedard (93)	26	Single Cohort	10 (100)	Self Pre-treatment	65.4 (21)	6.6(1.4)	Per
Engleman (93)	27	Parallel Cohort	21 and 16	Untreated SAHS	57(28) & 49(28)	6(4.6)	Per
Kribbs (93)	28	Single Cohort	15 (93)	Self Pre-treatment	56.6 (24.8)	2.5(1.7)	Psy; Per;S; QoL
Minemura (93)	29	Single Cohort	14 (100)	Self Pre-treatment	40 (20)	11(9) S	
Engleman (94)	30	Randomized Crossover	32 (81)	150 mg Ranitidine	28	1	Psy;Per;QoL
Borak (96)	31	Single Cohort	16 (100)	Self Pre-treatment	67 (16)	12	Psy;Per
Cassel (96)	32	Single Cohort	59 (100)	Self Pre-treatment	38.9 (3.4)	12	Per
Meurice (96)	33	Single Cohort	8 (100)	Self Pre-treatment	0.75		Per;S
Valencia-Flores (96)	34	Single Cohort	37 (78)	Self Pre-treatment	46.7 (32.4)	0.067	Per
Engleman (97)	35	Randomized Crossover	16 (75)	150 mg Ranitidine	11(4)	1	Psy;Per;S; QoL
Feuerstein (97)	36	Single Cohort	10 (100)	Self Pre-treatment	53.5 (24)	6.5 (1.3)	Per
Krieger (97)	37	Single Cohort	547 (87)	Self Pre-treatment	61.3 (25)	12	Per
George (97)	38	Parallel Cohort	18 and 17(100)	Untreated without SAHS	73 (28.9)	9.2(4.2)	Per
Bolitschek (98)	39	Parallel Cohort	16 and 67	Untreated SAHS	47.8(18.4)	3	QoL
Engleman (98)	40	Randomized Crossover	23 (91)	Placebo tablet	43 (37)	1	Psy;Per; S; QoL
Kotterba (98)	41	Single Cohort	15 (100)	Self Pre-treatment	36.9 (23.8)	6	Per
Meurice (98)	42	Single Cohort	9(100)	Self Pre-treatment	60.4(22.8)	0.7	Per
Naegele (98)	43	Single Cohort	10(100)	Self Pre-treatment	53.5(24)	6.5	Per
Redline (98)	44	Randomized Control	97 (52)	Nasal Strips	13.3 (9.8)	2.5 (.067)	Psy;S
Ballester (99)	45	Randomized Control	105 (88)	Sleep hygiene/ weight loss	56 (20)	3	S;QoL
D'Ambrosio (99)	46	Single Cohort	29 (79)	Self Pre-Test	77 (9)	2	QoL
Engleman (99)	47	Randomized Crossover	34 (62)	Placebo Tablet	10 (3)	1	Psy;Per;S;QoL
Jenkinson (99)	48	Randomized Control	107 (100)	Subtherapeutic CPAP	33 (CI 6-72)	1	S; QoL

Psy= Psychological Assessment; Per=Performance Assessment; S=Sleepiness; QoL=Quality of Life

assessment as defined by the intent of the authors. Thirty-six different instruments were used to evaluate these parameters.

Six of the 19 studies used a comparison group other than the pre CPAP treatment state. Two of the 6 studies^{30,38,49} demonstrated an overall significant improvement in performance assessment. Seven of the 13 single cohort studies demonstrated a significant performance

assessment improvement.^{24,26,31,32,37,41,42} No decline in performance assessment was reported following the addition of CPAP treatment.

Psychological Assessment

Nine studies evaluated the impact of CPAP on psychological assessment. Eleven different instruments were used to assess psychological status and, in addition, the

performance on numerous subscales was reported separately. The Hospital Anxiety and Depression Scale was the most frequently used assessment tool.^{30,35,40,47} The Profile of Mood was administered in 2 studies^{23,28} but was used differently in each. In one, only results on 2 subscales were assessed, while in the other study all 6 subscales and an overall total score were assessed and analyzed. The remaining 9 instruments were not used in more than 1 study.

Six of the studies used a comparison group for CPAP treatment other than the pretreatment state. Three^{23,30,44} demonstrated an overall significant improvement in psychological performance, while 2 were inconclusive.^{35,47} Depression and anxiety were the subscales of psychological assessment most frequently measured. Five of 8 studies demonstrated a statistically significant improvement in performance on a depression scale, and 1 of 6 studies on an anxiety scale. No study reported a decline in psychological performance following treatment with CPAP.

Sleepiness

Eight studies reviewed the impact of CPAP on subjective sleepiness. Four instruments were used to measure sleepiness: 1) the Epworth Sleepiness Scale (a measure of the propensity to fall asleep), 2) the Stanford Sleepiness Scale (a subjective evaluation of sleepiness), 3) the UTWIST Mood Adjective checklist, and 4) the Psychomotor Vigilance Task. The Epworth Sleepiness Scale was used in 6 studies; the Stanford Sleepiness Scale and the UTWIST Mood Adjective checklist were each used in two.

The Epworth Sleepiness Scale demonstrated a statistically significant improvement in 5 studies, the Stanford Sleepiness Scale in two and the Psychomotor Vigilance Task in one. Only 1 study¹³ failed to demonstrate an improvement in subjective sleepiness with any scale. This study used a randomized crossover design with 16 subjects with a mean AHI of 11 and the follow up evaluation at 1 month. No study reported a worsening of subjective sleepiness following the administration of CPAP therapy.

Quality of Life

Quality of life was assessed in 9 studies. Four different instruments, the Nottingham Health Profile Part 2 (NHP-P2), the Sickness Impact Profile, the Munich Life Questionnaire, and the Medical Outcome Study SF-36, were utilized in these studies. The Nottingham Health Profile Part 2 was the instrument used most frequently. Six studies used a comparison group for CPAP treatment other than the pretreatment self state.^{30,35,39,40,47,48}

Three studies demonstrated an overall statistical improvement in quality of life, two demonstrated no impact on subscales of the SF-36, and four were inconclusive. One study,³⁵ which failed to show an improvement in quality of life, noted that in a subset analysis that the quality of life improved significantly in the group with greater CPAP compliance (5 ± 0.6 hours versus 1.1 ± 0.2 hours, $p < 0.05$). No study reported a significant decline in quality of life following CPAP treatment.

DISCUSSION

CPAP efficacy has been the focus of statement papers,³ review articles,⁵⁰ and numerous clinical investigations. Such publications have a profound impact on clinical practice and research. Systematic reviews address a sharply defined clinical question, summarize the data, and therefore help refine research hypotheses and goals. We performed this systematic review to frame what is known about the neurobehavioral performance of patients with obstructive sleep apnea following CPAP therapy.

A systematic review may be qualitative or quantitative. A qualitative review summarizes the results of the primary studies but does not combine the results for statistical analysis. A quantitative review, also referred to as a meta-analysis, uses statistical methods to combine the results of primary studies, provided primary study design heterogeneity does not complicate the successful integration of data. Three forms of heterogeneity:⁵¹ 1) diverse study designs, 2) numerous instruments used to measure response to therapy, and 3) broad duration of CPAP therapy, prevented integrating the primary study data into a quantitative review. This current systematic review is, therefore, a qualitative review summarizing, but not integrating, the data presented in the 26 studies included in this review.

Sleepiness was the most consistently evaluated of the 4 outcome parameters researched. The evidence suggested that self-reported sleepiness improves following therapy. Sleepiness failed to significantly improve in 1 study³⁵ of patients with "mild disease." These same authors later published a study in which the AHI and treatment duration were similar to the former study but with twice the number of participants. This subsequent study did demonstrate improved sleepiness following CPAP treatment,⁴⁷ suggesting that the first study lacked sufficient power to detect a change.

This review suggests health-related quality of life (HRQOL) may improve following CPAP therapy, and that the improvement is sensitive to both compliance

and duration. The primary studies measured overall (generic) HRQOL. Generic HRQOL instruments are expected to be less sensitive to changes in HRQOL attributable to OSAH treatment, than would disease specific instruments such as the Functional Outcomes of Sleep Questionnaire⁵² and the Calgary Sleep Apnea Quality of Life Index.⁵³ Failure to detect a significant change in HRQOL was associated with a treatment duration of 1 month,^{35,40,47} whereas those detecting improvement had a treatment of 1 month or more.^{28,30,39} This suggests that changes in HRQOL may be sensitive to treatment duration. It is also evident that improvement in HRQOL is sensitive to CPAP compliance. Engleman performed a subgroup analysis and noted that HRQOL improved significantly in the group with greater compliance (mean use of CPAP for 5 ± 0.6 hours), compared to the noncompliant group (mean use of CPAP of 1.1 ± 0.2 hours).³⁵ Redline also noted that greater compliance was associated with a greater likelihood of treatment response.⁴⁴ Finally, using a generic measure of HRQOL, Engleman noted that better CPAP compliance resulted in a greater treatment effect size though this did not reach statistical significance.⁴⁷

Two outcomes of psychological assessment—fatigue and depression—responded favorably to CPAP therapy. Three studies^{23,28,44} reported a significant improvement in fatigue following 2 months or more of CPAP treatment. The outcome depression significantly improved in several studies.^{23,25,30,35,47} While failing to do so in a few,^{28,31,40} there was no difference with respect to therapy duration, subject number, or study design from those that did and did not detect an improvement in depression. The impact of CPAP on other outcomes of psychological assessment such as anxiety is not clear, in large part due to the diverse ways these parameters were evaluated.

Performance assessment was addressed as either 1) driving performance,^{24,32,38,49,54} 2) cognition,⁴⁰ 3) vigilance,³⁰ or 4) attention capacity.³⁵ There was significant improvement in simulated driving performance and the number of automobile accidents and near accidents following CPAP therapy. Vigilance when evaluated a priori demonstrated a significant improvement following CPAP therapy.

Finally, memory efficiency—long-term memory or short-term memory—failed to significantly improve following CPAP therapy. This may not be unexpected given that a large population-based study did not detect an association between OSAHS and memory deficit.⁵⁵ The more complex functions such as memory and executive function are felt to be more affected by hypox-

emia.⁵⁶ The level or duration of pretreatment hypoxemia endured by the subjects in these studies is unknown.

This review may be viewed as having limitations that may bias the conclusions in favor of “CPAP therapy having no impact on neurobehavioral outcome in OSAHS.” First, the effect is reported as either “significant or not” instead of in standard deviation units (effect size). Significance tests are intended solely to address the viability of the null hypothesis that a treatment has no effect, whereas the effect size estimates the magnitude (mild, moderate, large) of the treatment effect.⁵⁷ In this review, studies with treatment effects of 0.6 or greater⁵⁸ (data not shown) for the most part demonstrated a statistically significant improvement in test performance and as a result were designated as a “+” effect. The cases in which a large effect size did not correlate with statistical significance involved studies inadequately powered to reach statistical significance. Therefore, in a few cases in which a moderate to large treatment effect size was detected, but the change did not reach statistical significance, these were reported as “no change.” Second, this review did not combine data as would be done in a quantitative review. The possibility exists that studies with inconclusive results, when analyzed separately, would have attained significance if evaluated in aggregate. Third, this review cannot address the impact that sleep fragmentation, arousals, and hypoxemia have on neurobehavioral performance, as this information could not be abstracted from the reported data. Finally the robustness of the results might be called into question because studies other than randomized controlled trials were included. If the seven randomized trials^{30,35,40,44,45,47,48} were the only trials considered, the conclusions would require slight modification. There would be less evidence that CPAP has a significant impact on generic health-related quality of life, there would be more support for CPAP having a significant impact on depression, and finally fewer psychological and performance assessment studies would be available for analysis. In addition, recent randomized trials have shown improved quality of life, but otherwise support the above conclusions.⁵⁹⁻⁶⁵

This qualitative systematic review supports the assertion that CPAP has a significant and positive impact on: 1) subjective sleepiness, and 2) depression when randomized controlled trials are considered and additionally on 3) fatigue, 4) generic health-related quality of life, 5) vigilance, and 6) driving performance when all prospective trials are considered. These parameters appear to be sensitive to the duration of (>1 month) and

compliance with therapy. These results should be considered when developing health policy and designing future clinical trials.

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REFERENCES

1. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993; 328:1230-1235.
2. Young T, Hutton R, Finn L, et al. The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? *Arch Intern Med.* 1996; 156:2445-2451.
3. American Thoracic Society/American Sleep Disorders Association. Statement on health outcomes research in sleep apnea. *Am J Respir Crit Care Med.* 1998; 157:335-341.
4. Nosedá A, Kempnaers C, Kerkhofs M, et al. Sleep apnea after 1 year domiciliary nasal-continuous positive airway pressure and attempted weight reduction. Potential for weaning from continuous positive airway pressure. *Chest.* 1996; 109:138-143.
5. Watson RK, Thompson AS. Treatment outcome of sleep apnea. *Conn Med.* 1992; 56:125-129.
6. Wedel MK, van Dyne BJ, Berman TM. Treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) by nasal mask. *Minn Med.* 1984; 67:553-554.
7. Sanders MH, Gruendl CA, Rogers RM. Patient compliance with nasal CPAP therapy for sleep apnea. *Chest.* 1986; 90:330-333.
8. Remmers JE, Sterling JA, Thorarinsson B, et al. Nasal airway positive pressure in patients with occlusive sleep apnea. Methods and feasibility. *Am Rev Respir Dis.* 1984; 130:1152-1155.
9. Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnea syndromes. American Thoracic Society. Official statement adopted March 1944. *Am J Respir Crit Care Med.* 1994; 150:1738-1745.
10. Strollo PJ, Jr., Sanders MH, Atwood CW. Positive pressure therapy. *Clin Chest Med.* 1998; 19:55-68.
11. Laursen SB, Dreijer B, Hemmingsen C, et al. Bi-level positive airway pressure treatment of obstructive sleep apnoea syndrome. *Respiration.* 1998; 65:114-119.
12. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. American Sleep Disorders Association. *Sleep.* 1995; 18:511-513.
13. Schmidt-Nowara W, Lowe A, Wiegand L, et al. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep.* 1995; 18:501-510.
14. Practice parameters for the treatment of obstructive sleep apnea in adults: the efficacy of surgical modifications of the upper airway. Report of the American Sleep Disorders Association. *Sleep.* 1996; 19:152-155.
15. Weaver TE, Kribbs NB, Pack AI, et al. Night-to-night variability in CPAP use over the first three months of treatment. *Sleep.* 1997; 20:278-283.
16. Rauscher H, Formanek D, Popp W, et al. Self-reported vs measured compliance with nasal CPAP for obstructive sleep apnea. *Chest.* 1993; 103:1675-1680.
17. Meurice JC, Dore P, Paquereau J, et al. Predictive factors of long-term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. *Chest.* 1994; 105:429-433.
18. Krieger J. Long-term compliance with nasal continuous positive airway pressure (CPAP) in obstructive sleep apnea patients and nonapneic snorers. *Sleep.* 1992; 15:S42-S46.
19. Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. *Thorax.* 1994; 49:263-266.
20. Block AJ, Boysen PG, Wynne JW, et al. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance. *N Engl J Med.* 1979; 300:513-517.
21. Practice parameters for the indications for polysomnography and related procedures. Polysomnography Task Force, American Sleep Disorders Association Standards of Practice Committee. *Sleep.* 1997; 20:406-422.
22. Slavin RE. Best evidence synthesis: an intelligent alternative to meta-analysis. *J Clin Epidemiol.* 1995; 48:9-18.
23. Derderian SS, Bridenbaugh RH, Rajagopal KR. Neuropsychologic symptoms in obstructive sleep apnea improve after treatment with nasal continuous positive airway pressure. *Chest.* 1988;94:1023-1027.
24. Findley LJ, Fabrizio MJ, Knight H, et al. Driving simulator performance in patients with sleep apnea. *Am Rev Respir Dis.* 1989;140:529-530.
25. Ramos Platon MJ, Espinar SJ. Changes in psychopathological symptoms in sleep apnea patients after treatment with nasal continuous positive airway pressure. *Int J Neurosci.* 1992;62:173-195.
26. Bedard MA, Montplaisir J, Malo J, et al. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). *J Clin Exp Neuropsychol.* 1993;15:330-341.
27. Engleman HM, Cheshire KE, Deary IJ, et al. Daytime sleepiness, cognitive performance and mood after continuous positive airway pressure for the sleep apnoea/hypopnoea syndrome. *Thorax.* 1993;48:911-914.
28. Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis.* 1993;147:1162-1168.
29. Minemura H, Akashiba T, Yamamoto H, et al. [Traffic accidents in obstructive sleep apnea patients and effect of nasal CPAP treatment]. [Japanese]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1993; *Japanese Journal of Thoracic Diseases.* 31:1103-1108.
30. Engleman HM, Martin SE, Deary IJ, et al. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet.* 1994;343:572-575.
31. Borak J, Cieslicki JK, Koziej M, et al. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. *J Sleep Res.* 1996;5:123-127.
32. Cassel W, Ploch T, Becker C, et al. Risk of traffic accidents in patients with sleep-disordered breathing: reduction with nasal CPAP. *Eur Respir J.* 1996;9:2606-2611.
33. Meurice JC, Marc I, Series F. Efficacy of auto-CPAP in the treatment of obstructive sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med.* 1996;153:794-798.
34. Valencia-Flores M, Bliwise DL, Guilleminault C, et al. Cognitive function in patients with sleep apnea after acute nocturnal nasal continuous positive airway pressure (CPAP) treatment: sleepiness and hypoxemia effects. *J Clin Exp Neuropsychol.* 1996;18:197-210.

35. Engleman HM, Martin SE, Deary IJ, et al. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax*. 1997;52:114-119.
36. Feuerstein C, Naegele B, Pepin JL, et al. Frontal lobe-related cognitive functions in patients with sleep apnea syndrome before and after treatment. *Acta Neurol Belg*. 1997;97:96-107.
37. Krieger J, Meslier N, Lebrun T, et al. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: a prospective study. *Chest*. 1997;112:1561-1566.
38. George CF, Boudreau AC, Smiley A. Effects of nasal CPAP on simulated driving performance in patients with obstructive sleep apnoea. *Thorax*. 1997; 52:648-653.
39. Bolitschek J, Schmeiser-Rieder A, Schobersberger R, et al. Impact of nasal continuous positive airway pressure treatment on quality of life in patients with obstructive sleep apnoea. *Eur Respir J*. 1998; 11:890-894.
40. Engleman HM, Martin SE, Kingshott RN, et al. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax*. 1998; 53:341-345.
41. Kotterba S, Rasche K, Widdig W, et al. Neuropsychological investigations and event-related potentials in obstructive sleep apnea syndrome before and during CPAP-therapy. *J Neurol Sci*. 1998; 159:45-50.
42. Meurice JC, Paquereau J, Denjean A, et al. Influence of correction of flow limitation on continuous positive airway pressure efficiency in sleep apnoea/hypopnoea syndrome. *Eur Respir J*. 1998; 11:1121-1127.
43. Naegele B, Pepin JL, Levy P, et al. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. *Sleep*. 1998; 21:392-397.
44. Redline S, Adams N, Strauss ME, et al. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *Am J Respir Crit Care Med*. 1998; 157:858-865.
45. Ballester E, Badia JR, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med*. 1999; 159:495-501.
46. D'Ambrosio C, Bowman T, Mohsenin V. Quality of life in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure—a prospective study. *Chest*. 1999; 115:123-129.
47. Engleman HM, Kingshott RN, Wraith PK, et al. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. *Am J Respir Crit Care Med*. 1999; 159:461-467.
48. Jenkinson C, Davies RJ, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet*. 1999; 353:2100-2105.
49. Dinges DF, Kribbs NB, Schwartz AR, et al. Objective measurement of nasal continuous positive airway pressure use. Ethical considerations. *Am J Respir Crit Care Med*. 1994; 149:291-292.
50. Wright J, Johns R, Watt I, et al. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ*. 1997; 314:851-860.
51. Mulrow C, Langhorne P, Grimshaw J. Integrating heterogeneous pieces of evidence in systematic reviews. *Ann Intern Med*. 1997; 127:989-995.
52. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997; 20:835-843.
53. Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med*. 1998; 158:494-503.
54. Sartoris DJ, Neumann CH, Riley RW. The temporomandibular joint: true sagittal computed tomography with meniscus visualization. *Radiology*. 1984; 150:250-254.
55. Kim HC, Young T, Matthews CG, et al. Sleep-disordered breathing and neuropsychological deficits. A population-based study. *Am J Respir Crit Care Med*. 1997; 156:1813-1819.
56. Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. *Sleep*. 1987; 10:254-262.
57. Borenstein M. Hypothesis testing and effect size estimation in clinical trials. *Ann Allergy Asthma Immunol*. 1997; 78:5-11.
58. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol*. 1995; 48:71-79.
59. Barbe F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med*. 2001; 134:1015-1023.
60. Bardwell WA, Ancoli-Israel S, Berry CC, et al. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: a placebo-controlled study. *Psychosom Med*. 2001; 63:579-584.
61. Hack MA, Choi SJ, Vijayapalan P, et al. Comparison of the effects of sleep deprivation, alcohol and obstructive sleep apnoea (OSA) on simulated steering performance. *Respir Med*. 2001; 95:594-601.
62. Henke KG, Grady JJ, Kuna ST. Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypopnea syndrome. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2001; 163:911-917.
63. Montserrat JM, Ferrer M, Hernandez L, et al. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. *Am J Respir Crit Care Med*. 2001; 164:608-613.
64. Sanner BM, Klewer J, Trumm A, et al. Long-term treatment with continuous positive airway pressure improves quality of life in obstructive sleep apnoea syndrome. *Eur Respir J*. 2000; 16:118-122.
65. Scharf MB, Stover R, McDannold MD, et al. Outcome evaluation of long-term nasal continuous positive airway pressure therapy in obstructive sleep apnea. *Am J Ther*. 1999; 6:293-297.



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