REVIEW

# Evaluation of Positive Airway Pressure Treatment for Sleep Related Breathing Disorders in Adults

## A Review by the Positive Airway Pressure Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine

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**Abstract:** Positive airway pressure (PAP) is used to treat obstructive sleep apnea (OSA), central sleep apnea (CSA), and chronic hypoventilation. This document provides a systematic analysis and grading of peer-reviewed, published clinical studies pertaining to application of PAP treatment in adults. The paper is divided into 5 sections, each addressing a series of questions. The first section deals with whether efficacy and/or effectiveness have been demonstrated for continuous PAP (CPAP) treatment based on a variety of parameters and the level of OSA severity. Next, CPAP titration conducted with full, attended polysomnography in a sleep laboratory is compared with titration done under various other conditions. The third section investigates what can be expected regarding adherence and compliance with CPAP treatment as measured by subjective and objective methods and what factors may influence these parameters. Side effects and the influence of other specific factors on efficacy, effectiveness and safety of CPAP therapy are evaluated in the fourth section. Finally, the use of bilevel PAP therapy is reviewed for both patients with OSA and those with other selected nocturnal breathing disorders. Each section also contains a brief summary and suggestions for future research.

**Keywords:** Sleep related breathing disorder, obstructive sleep apnea; continuous positive airway pressure; CPAP; sleep disordered breathing; bilevel positive airway pressure, BiPAP

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### 1.0 INTRODUCTION

POSITIVE AIRWAY PRESSURE (PAP) APPLIED THROUGH A NASAL, ORAL, OR AN ORONASAL INTERFACE DURING SLEEP IS THE PREFERRED TREATMENT FOR obstructive sleep apnea (OSA), but may also be used for some patients with central sleep apnea (CSA) and chronic hypoventilation. Types of PAP treatment include continuous PAP (CPAP), bilevel PAP, and automatic adjusting PAP (APAP). The literature evaluating APAP was recently evaluated in a systematic review and will not be considered in this review.[1]

The most widespread application of PAP is the treatment of OSA with CPAP. Untreated OSA may result in a variety of well-known symptoms including increased daytime sleepiness, impaired neurobehavioral performance, decreased quality of life and increased risk for cardiovascular disease (most studies have focused on hypertension). A systematic review of the current CPAP treatment outcome literature provides a basis for best clinical practice and helps direct future research efforts. We also reviewed the literature supporting various techniques to titrate CPAP to the optimal pressure setting. We attempted to answer questions such as, "How will the outcomes from a technologist attended CPAP titration with a standard polysomnogram (PSG) differ from unattended or partial montage PSG?" We also asked, "What factors impact CPAP treatment acceptance and adherence including treatment delay, adherence monitoring, disease severity, equipment type, and side effects?"

Treatment of CSA and hypoventilation with PAP is less studied and established than treatment of OSA. The prevalence of other sleep related breathing disorders (SRBDs) in many sleep clinic populations is less than OSA; this may explain the relative paucity of data. For this reason, treatment of SRBDs other than OSA are not addressed in detail in this review except as they pertain to the use of bilevel PAP treatment. The use of PAP in the treatment of heart failure is also not included in this review.

Nocturnal bilevel PAP treatment is also used to treat adult patients with hypoventilation from chronic obstructive pulmonary disease (COPD), neuromuscular diseases, and chest wall disease such as kyphoscoliosis. Pressure titration methods, treatment adherence, side effects and treatment outcomes will also be systematically reviewed for this heterogeneous group of patients with SRBDs.

### 2.0 METHODOLOGY

A task force was assigned by the Standards of Practice Committee (SPC) of the American Academy of Sleep Medicine (AASM) for the purpose of developing a review of the literature pertaining to the treatment of SRBDs in adults with PAP. The project was initiated in the fall of 2000 with the formulation of questions as identified under each section, followed by the construction of an extraction worksheet and the development of evidence table format. Although 6 abstractors were part of the initial effort, the final document was written by 4 authors who were actively involved

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**Table 1**—AASM Classification of Evidence

| Evidence Levels | Study Design |
|---|---|
| I | Randomized well-designed trials with low alpha and beta error* |
| II | Randomized trials with high alpha and beta error* |
| III | Nonrandomized concurrently controlled studies |
| IV | Nonrandomized historically controlled studies |
| V | Case series |

Adapted from Sackett[3]
*Alpha error refers to the probability (generally set at 95% or greater) that a significant outcome (e.g., $p<0.05$) is not a result of chance occurrence. Beta error refers to the probability (generally set at 80% to 90% or greater) that a nonsignificant result (e.g., $p > 0.05$) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis to project the size of the study population necessary to ensure that significant differences will be observed if actually present.

throughout the entire project. This review provided the necessary data for the development of the companion practice parameters by the SPC.

The level of evidence for the data in each paper relevant to the evaluation is listed in evidence tables specific for each question. Each paper was analyzed independently by 2 task force members. The level of evidence was rated using the AASM classification of evidence for intervention studies (Table 1), an adaptation of the Sackett criteria.[2] Disagreements between the 2 raters were adjudicated by a vote of the task force members.

Searches in the English language literature (Medline 1966 - early 2005) of major topics relevant to PAP treatment during SRBDs were conducted. The initial literature search was done in April of 2001 followed by an update in April of 2002. A final literature search for just Level I studies was done in January of 2005 in order to keep the review as timely as possible and to avoid omission of potentially high impact studies published in the interim. The decision to limit the final search and some entire sections to Level I or II evidence was decided upon by the Task Force for the purposes of simplification and brevity. The Task Force did not feel this would detract from the overall conclusions made within the body of this review. The search focused on peer-reviewed clinical studies, including case-series and controlled trials, which contained information regarding PAP treatment outcomes, methods for polysomnographic titration, factors affecting adherence and side effects. Major search terms are included as Table 2. Review papers, commentary, case reports, pediatric populations, and studies pertaining to APAP were excluded, except where parenthetical comments are specifically noted. Comments are provided when necessary to emphasize where lack of a power analysis, clearly designated primary endpoint, or small sample size may have confounded the conclusions.

Some questions used all levels of evidence whereas others were confined to specific levels of evidence as noted in each section. OSA now has well-recognized associations with many other systemic effects, especially cardiovascular effects; a comprehensive, detailed discussion of all is beyond the scope of this paper. For this reason, our review was confined to the best-studied cardiovascular issue associated with OSA (hypertension) and the effect of PAP treatment. Five major questions are detailed and discussed in this review paper; a summary and suggestions for future research appear at the end of each section.

**Table 2**—Literature Search Terminology and Keywords

**Mesh Terms**
Sleep apnea syndromes
Positive-pressure respiration
Congestive heart failure
Obstructive lung diseases

**Text Words**
Apnea
Obstructive sleep apnea
Central sleep apnea
Cheyne-Stokes respiration
Hypopnea
Sleep apnea-hypopnea syndrome
Upper airway resistance syndrome
Sleep-disordered breathing
Chronic hypoventilation
Chronic respiratory failure
COPD
CPAP
Positive airway pressure
Nocturnal ventilation
Positive pressure therapy
Sleepiness
Hypertension
Bipap
Bilevel positive airway pressure
Polysomnography
Oximetry
Ambulatory monitoring
Split-night study

### 3.1 Has Efficacy and/or Effectiveness Been Demonstrated for CPAP Treatment in Patients with OSAHS?

The literature search identified 342 articles that met the extraction criteria discussed in Section 2.0. Only investigations that were randomized controlled clinical trials and considered Level I or II evidence, compared CPAP to placebo or conservative treatment (nasal strips, weight loss, sleep hygiene, positional therapy), and that employed generally accepted and validated endpoints were included in the review. Of these 29 studies,[3-31] 45% compared CPAP to sham-CPAP,[4,5,7,8,15-17,22,25-27,29,30] 31% used tablets as placebos,[6,9-14,23,31] and 24% compared CPAP to conservative treatment.[3,18-21,24,28] Of the randomized controlled clinical trials that evaluated adherence to both placebo and active CPAP interventions and reported hours of use, mean nightly active CPAP use was 4.46 hrs[3-7,9-18,23-26,28,29,31,32] compared to 4.85 hrs on sham-CPAP.[3-5,7,15-17,25,26,29] Most of the randomized controlled clinical trials assessed multiple outcomes, but only 28% of the studies specified a primary endpoint.[4,7,8,20,24-26,31] Based on Spilker's definition of a double blinded study (neither the investigator following the participant nor the participant were aware of treatment assignment[33]), few clinical trials were double blinded[16,17,21,22,26,30] which can possibly introduce unintended bias. There were a number of controlled clinical trials that published negative findings, but failed to include a power analysis introducing the probability of a Type II error.[5,8,9,16,22,27,29,30,34] Of the 29 clinical trials, 11 studies performed Intent-To-Treat analysis[3-5,13,18,24,26,34] and only 3[6,10,17]

provided effect sizes to characterize the magnitude of the impact of CPAP on the outcomes under consideration.

We examined the efficacy of CPAP for the following outcomes: apnea/hypopnea index (AHI), considered synonymous with respiratory disturbance index (RDI), sleep architecture, daytime sleepiness, quality of life, neurobehavioral performance and psychological effects, and cardiovascular morbidity (hypertension).

### 3.1.1 Reduction of Apnea/Hypopnea Index

In general, the literature documents that CPAP eliminates respiratory disturbances, reducing the AHI. All of the 11 clinical trials that studied this outcome demonstrated that CPAP was superior to placebo,[5,7,8,16,22,29-31] conservative management,[24,28] and positional therapy.[18] This effect was demonstrated during follow-up polysomnography (PSG) after 16[16] or 65 days[7]; 1,[5,8,22,29,30] 2,[18] 10,[28] or 24[24] weeks; or 3 months[31] of intervention.

### 3.1.2 Sleep Architecture

The results of controlled clinical trials do not provide support that CPAP affects total sleep time when compared to placebo[5,7,22,31] or positional therapy.[18] The evidence supporting the effect of CPAP on duration and proportion of stage 1 or 2 sleep is mixed with several placebo controlled trials demonstrating a positive effect,[22,23,31] whereas other studies did not.[5,7] There was also no significant difference shown in stage 1 or 2 sleep between positional therapy and CPAP.[18] Two placebo-controlled studies found a difference in length of time in REM sleep[5,22] but this was not true when CPAP efficacy was compared with positional therapy.[18] Three[22, 23,31] of the 5 placebo-controlled studies[5,7,22,23,31] reported improvements in stage 3 or 4 sleep. As with the other stages of sleep, there was no difference in stage 3 or 4 sleep when CPAP was compared with positional therapy.[18] Several randomized clinical trials found that active treatment was no better than placebo[5,22,31] or positional therapy[18] in affecting the amount of time awake or sleep efficiency. There is inconsistent support for the effect of CPAP on arousal index. However, several Level I and II studies provided evidence of a lower arousal index with CPAP compared to placebo,[22,23,31] and only 1 study did not.[7]

### 3.1.3 Daytime Sleepiness

There has been considerable study of the impact of CPAP on subjective and objective daytime sleepiness. The majority of these studies have evaluated subjective sleepiness, principally using the Epworth Sleepiness Scale (ESS).[35] Of the placebo-controlled trials employing the ESS,[4,6,7,10,12-17,23,25,31] most found that CPAP reduced subjective daytime sleepiness.[7,10,13-15,17,23,25,31] The evidence that CPAP is superior to conservative or positional therapy is less compelling. Ballester and colleagues[3] noted improvements with CPAP use compared to conservative therapy (sleep hygiene, weight loss and diet). However, Monasterio and associates[24] used a similar intervention and Redline and coworkers[28] added nasal strips to conservative therapy and did not observe an improvement.

The Level I and II evidence for objective daytime sleepiness was more equivocal. For example, 2[15,17] of the 3 studies[4,15,17] that employed sham-CPAP and evaluated objective sleepiness using the Maintenance of Wakefulness Test found a greater effect for CPAP compared to the placebo. It should be noted that the sample in the negative study consisted of non-sleepy patients prior to intervention and measured objective sleepiness employing the Multiple Sleep Latency Test. However, when a tablet was used as the placebo to evaluate this effect, only 2[13,32] of 6 studies[6,10,12,13,31,32] showed that CPAP was the superior intervention. The 2 studies that compared CPAP to conservative treatment failed to detect significant differences between these treatments.[24,28]

### 3.1.4 Neurobehavioral Performance and Psychological Effects

Of the 29 placebo-controlled trials, 10[4-6,10,12,13,15,16,31,32] explored the impact of CPAP on neurobehavioral performance. Performance variables included cognitive processing, sustained attention, executive function, memory and mood. Only 2[10,11] of the 9 placebo-controlled studies that evaluated cognitive functioning[4-6,10-13,16,31] found CPAP superior to placebo. The studies were inconclusive with regard to the benefit of CPAP over placebo in improving sustained attention.[4-6,10-13,16,31] The 2 studies comparing conservative therapy to CPAP treatment produced conflicting results with regard to the impact on cognitive processing.[21,24] There were too few studies to draw conclusions regarding differences between conservative and CPAP therapy and change in sustained attention. The 1 study that evaluated positional versus CPAP therapy found that CPAP was superior to positional therapy for cognitive processing, but not sustained attention.[18] CPAP therapy was not superior to placebo[4,6,31] or positional therapy[18] for restoring memory. However, it was more effective than conservative therapy, such as sleep hygiene and weight loss.[21,24] Of the Level I and II investigations evaluating executive functioning,[4,5,10-13,31,36] few of these studies provided support that CPAP was more effective than placebo[4,5,10,13,31] or positional therapy.[18] There was only 1 Level I study that compared CPAP to conservative therapy with regard to executive functioning and it demonstrated a greater impact for CPAP.[24] Results from placebo-controlled studies were inconclusive with regard to the efficacy of CPAP in elevating mood.[6,10-13,29-31] Inconsistent results in neurobehavioral performance among studies may be related to the different measures employed to evaluate these outcomes as well as the likelihood of a beta error.

### 3.1.5 Quality of Life

A number of studies have compared the impact of CPAP relative to placebo,[4,6,10-14,17,25,27,34] conservative treatment[3,24,28] or positional therapy[18] on quality of life. These studies have employed both generic (SF36, Nottingham Health Profile) and disease-specific (Functional Outcomes of Sleep Questionnaire) measures. Among the Level I and II placebo-controlled investigations, the findings are inconclusive with equal numbers of positive[10-12,17,31] and negative[4,6,13,25,27] conclusions regarding the superiority of CPAP treatment. Three randomized studies compared CPAP with conservative therapy.[3,24,28] One study found improvement in 2 of the 6 subscales (social isolation and energy) of the Nottingham Health Profile, a generic measure of quality of life.[3] A second study that employed both a generic and a disease-specific measure[24] and a third study that used only a generic measure[28] did not find significant improvement. The 1 study that examined quality of life in patients randomly assigned to CPAP or positional therapy did not find that CPAP produced greater gains than positional therapy as measured by a generic quality of life measure.[37]

### 3.1.6 Cardiovascular Morbidity (Focus on Hypertension)

The effects of CPAP therapy on cardiovascular disease, especially hypertension, has been a target of several recent investigations.[4,6-9,14,24,26,30,31] The majority of placebo-controlled studies that employed at least 19 hours of ambulatory blood pressure monitoring did not find that CPAP improved mean arterial pressure.[4,6-9,14,31] However, several Level I and II studies found that CPAP did have a greater impact on nocturnal blood pressure than placebo[8,14,26] and 2 studies showed lower mean diastolic pressure in patients on CPAP compared to controls.[14,26] One Level I study demonstrated a large reduction in mean arterial blood pressure following those on anti-hypertensive medications,[26] and a Level II study suggested that change in 24 hour systolic, diastolic and mean arterial blood pressure following CPAP treatment was greater than placebo in those with more than 20 desaturations of 4% or more per hour of sleep. The 1 study that compared CPAP to conservative therapy (weight loss, diet and sleep hygiene) found that blood pressure measured by sphygmomanometer in CPAP patients was not different than in patients treated with conservative therapy.[24] The sole study that examined change in blood pressure associated with treatment in milder OSA using a tablet placebo failed to show differences between CPAP treatment and placebo.[4] The 2 Level II studies that evaluated the impact of CPAP versus placebo on heart rate produced conflicting results.[14,30] Therefore, the impact of CPAP treatment on cardiovascular risk and associated organ dysfunction in milder OSA is unknown.

### 3.1.7 OSA Severity – Relationship to Efficacy and/or Effectiveness

Most of the Level I and II studies of the efficacy of CPAP treatment have been conducted in patients with moderate (AHI 15 - 30) and severe (AHI > 30) disease as defined by the AASM.[38] The 3 Level I studies[24,28,31] and 3 Level II studies[6,10,12] that were restricted to patients with mild to moderate OSA found that CPAP reduced AHI[24,28,31] but did not improve objective sleepiness[6,10,12,24,28,31] or blood pressure.[6,24,31] Conflicting results were found for subjective measures of sleepiness,[6,10,12,24,28] neurobehavioral performance,[6,10,12,24,31] mood[6,10,12,24,28,31] and quality of life.[6,10,12,24,28,31] Thus, it remains unclear whether CPAP has utility across outcomes for this level of disease severity.

Other Level I and II studies using a higher criterion of disease severity (AHI > 30) have shown that, compared to placebo, CPAP reduces apneas and hypopneas,[5,8,16,22,29,30] increases time in REM sleep[5,22,29,30] and improves oxygenation.[5,16,22,29,30] There is inconsistent evidence for an effect of CPAP on other aspects of sleep architecture, subjective and objective sleepiness, neurobehavioral function, mood, quality of life and blood pressure.

There have been no published Level I or II investigations that compared outcomes of CPAP treatment concurrently among mild, moderate and severe OSA as defined by the AASM.[38]

There are no Level I or II studies that have examined the efficacy or effectiveness of CPAP treatment in OSA patient with an AHI < 5. There have been several Level III studies as described in a large review paper[39] that have examined the use of CPAP in Upper Airway Resistance Syndrome (with an AHI < 5) and in subjects with an AHI < 10. There is insufficient evidence to draw conclusions regarding the efficacy and/or effectiveness of CPAP treatment in this population.

### 3.2 Summary

The studies reviewed for this section document that CPAP eliminates respiratory disturbances, thereby reducing the AHI compared to placebo, conservative management or positional therapy. There was somewhat stronger evidence supporting improved Stage 3 and 4 sleep and decreased EEG arousals with CPAP vs placebo. However, whether CPAP yields significant consistent improvement in overall sleep architecture or fragmentation is less clear. There is equivocal evidence whether CPAP improves objective daytime sleepiness, neurobehavioral performance, psychological functioning and quality of life. The impact of CPAP on cardiovascular risk, especially hypertension, is largely mixed and the data for differences in the effectiveness of CPAP based on various levels of OSA severity remains unknown.

### 3.3 Future Research

There is a need for double-blinded CPAP studies that have a clearly defined primary outcome and include power analyses and effect size calculations. Studies that specifically examine OSA subgroups with respect to severity are particularly lacking.

### 4.1 If CPAP Titration is Done Under the Following Conditions, How Will it Differ From Full, Attended Polysomnography (PSG, 4.1.1) in a Sleep Laboratory?

There were 140 articles reviewed for this question. Ultimately, 28 articles were selected for review, including studies graded at all evidence levels but excluding those with less than 10 patients. There were 2 Level I, 2 Level II, no Level III, and 24 Level IV studies included in this review. No studies were available for sections 4.1.4, 4.1.5, and 4.1.7. Thirteen studies had no comparative findings but provided results regarding baseline condition, full night (FN) diagnostic PSG data and a second night of CPAP titration. Some studies were described in relation to APAP. These were the subject of an earlier AASM position paper,[1] and, for the purposes of this review, these data were not considered. The largest number of comparative studies (7) was for split night (SN) attended PSG. Pertinent study endpoints for this question consisted primarily of comparative effective CPAP levels required to resolve sleep related breathing disorders, effect on sleep quality, and compliance or adherence to therapy at variable lengths of time of treatment. The individual studies are described in the context of each specific aspect of the question as indicated above.

### 4.1.1 Full, Attended PSG in a Sleep Laboratory

Since the full, attended PSG in a sleep laboratory is the standard, we wanted to evaluate the reliability of this standard. We searched for studies that examined the repeatability of CPAP titration, or that examined issues that affect the variability of results of such titrations (position, time on treatment, etc.) Of the 13 studies,[40-52] all were rated at Level IV evidence and no comparative patient population for the purposes of this question was provided. Nine studies provided data regarding compliance and adherence rates to CPAP therapy. Nine studies discussed results of sleep quality although not all included both diagnostic and CPAP titration sleep staging. The studies ranged from 10 to 95 patients and either exclusively enrolled men or men were the majority (71 to 93%) with a mean age of 48.2 to 57 yrs.

Very few studies involved patients with mild disease; the range of the mean AHI from all of the studies was between 25 and 97.6 with most above 50. The effective CPAP pressure was between 8.1 to10 cm $H_2O$ with a reduction in mean AHI to a level of between 2 and 9.1 after CPAP titration. Adherence data were not always provided, but acceptance rates when available ranged from 74% to 93.7% at follow-up times of 21 to 784 days. Most studies relied on objective machine counters and use ranged from 4.7 to 7.6 hours per night. Detailed complication data were rarely reported.

Four reports focused on less commonly selected endpoints rather than comprehensively describing the typical results of 2 FN studies. One study looked at the identification of effective CPAP pressure during 3 repeated titration PSGs and found a reduction of 1 to 2 cm $H_2O$ after either 2 or 8 months but not at 20 months.[49] Another study evaluated the hysteresis of CPAP titration demonstrating that repeat downward adjustment during FN PSG resulted in lowering of the effective CPAP pressure from 9.5 to 8.9 cm $H_2O$; however, it did not provide adherence data, and information regarding sleep staging was available only at baseline. Most patients had severe OSA with mean baseline AHI of 40.5 that corrected to 4.8.[40] A third study assessed the effect of body position and rapid eye movement (REM) sleep state on the effective CPAP level in patients with severe sleep apnea and found that supine position was associated with the maximum CPAP requirements in 86.7% of patients.[46] Body position effects were related to body mass index (BMI), RDI, and REM sleep state. Lastly, a study of the effect of CPAP pressure consistency over 2 consecutive full nights of CPAP titration indicated no difference in a group of patients with moderate-severe OSAHS of AHI = 39.3, but these authors provided no adherence or sleep stage data.[52]

#### 4.1.2 Split-Night Study Attended Full PSG

One of the earliest reports of successful SN CPAP titration was published in 1984.[53] Of the 7 papers published since 1993 and reviewed for this section,[36,54-59] most (6) were rated as Level IV and 1 was rated as Level II. There were 5 studies that included adherence rates to CPAP therapy and 4 that provided data describing sleep quality, 1 with all PSG studies, 2 with the diagnostic PSG only and 1 with the CPAP titration night alone. One study noted the frequency of healthcare access and utilization following the introduction of CPAP treatment.

The highest Level II evidence study had groups that were not strictly comparable.[36] In this study involving 20 patients with severe OSA, a SN PSG was followed by a CPAP titration FN PSG 2 weeks later, where CPAP was readjusted in group 1 (lowered from an initial mean of 12 cm $H_2O$ to a mean 9.5) but was not changed in group 2 (initial mean of 12 cm $H_2O$ was maintained). There were no differences between groups in adherence (6.9 vs.6.4 hours per night), sleep quality, and improvement in Epworth sleepiness scale (ESS) at 2 to 4 weeks after titration. These findings might have been confounded by the 2-week delay between SN and FN CPAP titration and by a lowering of the effective CPAP pressure rather than being a true comparison of FN and SN full PSG CPAP pressures.

Long term adherence (22 to 27 months) was assessed in another cohort study that matched 2:1, FN:SN PSG for age (50 yr.), sex (80% men), AHI (49/hr), and ESS (15).[56] There was a reduction in TST, percent REM, and slow wave sleep during the diagnostic study with SN PSG compared to a FN PSG, but no difference in mean prescribed CPAP (8.5 vs. 9 cm $H_2O$) was noted between the methods. Five of 46 SN vs. 6 of 92 FN PSG patients that required retitration for effective CPAP levels to achieve an AHI < 10. There were no differences in symptom relief, clinic visits, nurse interventions per year, initial acceptance (78 vs. 79%) or ultimate adherence rates (6 vs. 6.2 hours per night) between the 2 titration techniques. An unusually long time transpired from time of diagnosis to initiation of CPAP therapy in both groups, averaging over 1 year. The overall CPAP use correlated with low total sleep time (TST) during the diagnostic PSG, and a high ESS at baseline regardless of titration method.

Two other large studies (> 50 patients) tested whether an adequate CPAP prescription could be established with a SN design as compared to a single subsequent FN CPAP titration PSG, but no adherence data was examined.[57,59] Patients were predominately male (over 80%), middle-aged (near 50 years), with either mild or very severe OSA (mean AHI = 23.6 or 76.7). In the study of severe OSA patients, no change in CPAP pressure was noted in 62% of patients, 22% with 2.5 cm $H_2O$ higher, and 6% with 5 cm $H_2O$ higher CPAP pressure needs with the FN titration.[57] There was no difference in the mean CPAP levels (13 vs. 14 cm $H_2O$) when the AHI was corrected to less than 5. As expected, TST on CPAP was much less with SN vs. FN (132.4 vs. 257 min.) but both sleep efficiency (SE) (89.4 vs. 95.6%) and percent REM sleep (24.1 vs. 22%) were similar. The other study of mild OSA patients showed a significantly lower CPAP at the end of the SN vs. FN CPAP titration (8.8 vs. 10.3 cm $H_2O$) but this differed significantly only for patients with AHI < 20.[59] The relative effects of sleep stages, SE, and TST on CPAP were essentially similar for the SN and FN CPAP titration as in the prior study above.

Two smaller retrospective matched cohort studies with FN diagnostic PSG looked at adherence at 1 to 2 months. The study involving more severe OSA patients (AHI approximately 65) revealed a high acceptance rate of near 85% with mean use of 4.8 hours per night at 41 to 55 days and a marked reduction in mean arousals from about 44 to near 10 per hour.[54] The study with fewer patients in each group (12), consisted of more women than most other studies (33%), and with milder OSA (AHI = 27) showed one of the lowest acceptance rates of 63% and overall adherence at 5.2 hours per night for SN vs. 3.8 hours per night for FN although this difference was not significant ($p = 0.29$).[58]

The last paper in this group prospectively followed 27 long-term patients with severe OSA (AHI = 63.6) after CPAP titration with SN PSG, and compared results to unmatched historical FN CPAP titration study patients. An effective SN CPAP level (AHI < 5) was obtained in 87% patients with an initial acceptance rate of 78%. At a mean of 285 days later, the acceptance remained high at 80% and an adherence rate of 6.7 hours per night that compared favorably to their FN historical controls with 77% acceptance at over 3 months and 51% of patients self-reporting use > 7 hours per night.[55]

#### 4.1.3 Daytime Study Attended Full PSG

There were only 2 studies reporting on daytime studies, and both were Level IV using a cohort design matched for age, sex, BMI, and OSA severity.[60,61] The larger study of 32 patients in each group (82% male; age 50 years) had more severe OSA (mean AHI > 60) and the nighttime diagnostic study was performed for

all "night" patients and half of the "day" patients, which were selected for variable reasons that were not clearly specified.[61] When comparing the CPAP titration techniques, there were no significant differences in the effective CPAP level, number of failures, or complete or partially successful titrations (88%) although there was a trend towards more complete success in the night vs. day titration group (84 vs. 69%). There was an unusually high mean AHI while on CPAP (day = 29.4 vs. night = 20.3) due to the relatively smaller overall success rates seen in other FN titration studies. The day titration group had significantly lower sleep time at effective CPAP (1 vs. 2.5 hours), lower and total sleep time (2.1 vs. 4.8 hours), higher sleep efficiency (75.8 vs. 65.2%) and a similar percentage of REM sleep. After at least 12 weeks, there was no difference in the number of patients never on CPAP (day = 22 vs. night = 31%) or in those with self-reported CPAP use > 5 nights per week (day = 66 vs. night = 59%). There were no clear predictors of successful daytime titration including AHI, lowest oxygen saturation, or BMI although there was a trend with higher baseline ESS (successful = 15.9 vs. unsuccessful = 10.2; p = .07).

The other CPAP day titration study was smaller with 14 patients matched similarly as above with very severe OSA (AHI > 80). All patients underwent a FN diagnostic study resulting in CPAP levels of 12 cm $H_2O$ for a treated mean AHI < 10 for both day and night CPAP titration. The time in bed was shorter for the day vs. night group during CPAP titration (386 vs. 488 min) but sleep efficiency (≥ 80%) was similar as were the sleep time and percentage REM sleep at effective CPAP. The authors did not indicate how many patients required repeat titration studies to achieve an effective CPAP level but patients were followed up after 1 week of CPAP use at home. About 85% of patients from each group used their CPAP showing significant improvement in daytime sleepiness. The objectively measured number of nights used was similar with a mean period near 4.5 hours per night. The authors of both studies concluded that this method was a viable alternative to nighttime CPAP delivery but neither offered factors that predicted higher likelihood of success with day titration.

#### 4.1.4 Home Study Attended Full PSG

No studies were available for review in these categories as data from portable monitoring equipment were excluded. The reader is referred to a recent position paper on portable sleep monitors for information.[62]

#### 4.1.5 Home Study Unattended Full PSG

No studies were available for review in these categories as data from portable monitoring equipment were excluded. The reader is referred to a recent position paper on portable sleep monitors for information.[62]

#### 4.1.6 Sleep Laboratory Study Attended Partial PSG

There were 2 studies evaluated for this category with 1 rated as Level IV and the other as Level I.[63,64] The higher level evidence paper utilized a FN hospital laboratory PSG for all subjects followed by a randomized FN PSG and compared respiratory monitoring alone on a respiratory ward to complete PSG in a sleep laboratory.[64] This study was designed to assess identification of optimal CPAP level by both methods but did not provide sleep data, compliance or adherence data. This group of moderately severe OSA patients (mean AHI approximately 50) showed no significant difference in effective CPAP levels (9.3 vs. 9.7 cm $H_2O$). In 1 patient full PSG monitoring led to a pressure 5 cm $H_2O$ less than with respiratory monitoring; in other patients pressures were within 2.5 cm $H_2O$.

The smaller study of 11 patients was done in a sleep laboratory and was attended by a technologist to assess the utility of forced oscillation (FO) technique for CPAP titration.[63] The authors did not report acceptance or adherence rates nor was actual sleep stage data provided. They concluded that the FO measurements did not disturb sleep and provided a quantitative index of airway obstruction during CPAP titration.

#### 4.1.7 Sleep Laboratory Study Unattended Partial PSG

No studies were available for review in these categories as data from portable monitoring equipment was excluded. The reader is referred to a recent position paper on portable sleep monitors for information.[62]

#### 4.1.8 Home Study Attended Partial PSG

One Level IV study reported the feasibility of home attended partial PSG for CPAP titration after an in-laboratory FN PSG diagnostic study.[65] This appeared to be a non-consecutive retrospective case series of 17 patients with moderately severe OSA (AHI = 52.1) many of whom were selected because they did not wish to return to the laboratory for another PSG. CPAP was titrated based on respiratory monitoring and snoring as determined by the home-based technologist. A mean effective CPAP level of 10.3 cm $H_2O$ was obtained and acceptance of CPAP was reported at 76% (13 of 17) with a very high adherence rate of 7.2 hours per night after a mean of 13.4 months.

#### 4.1.9 Home Study Unattended Partial PSG

There were 4 papers available for review in this section although none of them actually used any form of home PSG equipment. The true home study unattended partial PSG studies all used portable monitors which as noted earlier were excluded from this review having been reviewed by another task force.[62] For this review, there was 1 Level I study using patient adjustment but no home monitoring equipment and the 3 others were Level IV with 2 studies using predicted equations and 1 using empiric CPAP titration based on bed partner's observations.[66-68]

The Level I study[69] followed 18 primarily middle-aged males with more severe apnea (age = 50 years, AHI = 40) in a randomized crossover trial each of 5 weeks comparing standard in-laboratory CPAP titration to patient CPAP home self-adjustment. Patients were instructed to alter the CPAP pressure in response to issues suggesting excessive or inadequate pressure levels with no sleep monitoring. The primary outcome was optimal CPAP pressure level with high patient adherence rate for relief of apnea and hypopnea, improved sleep quality, and resolution of symptoms. The optimal CPAP levels were identical near 10 cm $H_2O$ with maximum deviation of > 2 cm $H_2O$ in only 3 patients and similar mean adherence near 6.5 hours. There was equal and significant improvement in AHI (both means were 6 or less) as well as equivalent response in objective and subjective symptom and performance parameters (see evidence table for details). The authors concluded that in selected cases, home CPAP titration might

be feasible and allow elimination of a second laboratory-based PSG. The study could be criticized for a high dropout rate (6 of 24 or 25% of enrolled patients) and small patient numbers. There was also no improvement in sleep architecture for either treatment arm although baseline sleep efficiency was at or above 80% and percent of REM sleep was near or above 20% during the laboratory based PSGs.

The smallest study of 11 patients used an unattended home diagnostic study (baseline RDI = 41) to titrate beginning with CPAP of 5 and increasing by 2.5 cm $H_2O$ until snoring and other symptoms improved.[66] Repeat unattended home study indicated resolution to a normal mean AHI = 2.4. After 18 months, all patients reported good adherence with therapy although no details were given.

A much larger study used an initial cohort of 38 patients to derive a prediction equation for effective CPAP levels and then applied it prospectively to a group of 208 consecutive patients after a full-night laboratory-based diagnostic PSG, which revealed moderate to severe OSA (AHI = 50).[67] The CPAP derived from the prediction equation agreed closely with that obtained during an additional laboratory PSG in a confirmation group of 129 patients (8 vs. 8.1 cm $H_2O$). When separating groups into high (> 10 cm $H_2O$) and low (< 5 cm $H_2O$) CPAP needs, the most important determining factors included AHI, BMI, and neck circumference. Although no sleep stage or adherence data were given, the authors concluded that prediction equations might be used to simplify empiric determinations of best CPAP level to use in the laboratory or at home and perhaps reduce the time to obtain the effective CPAP level.

This same approach was later tested by 1 of the authors as he and others prospectively studied 329 predominately male patients with diagnostic FN lab PSG (AHI > 10 [mean AHI = 47]).[68] After a laboratory-based FN PSG CPAP titration, they segregated the patients into those who had a successful effective CPAP level predicted by the equation with both pressures within 2 cm$H_2O$ (84%), were over-predicted (13%), or were under-predicted (3%). The group that had an over-prediction of effective CPAP tended to be significantly less overweight and had milder sleep apnea. Patients that were under-predicted included those with significant central sleep apnea, poor sleep at higher CPAP pressures or major mask leaks. The investigators did not provide any sleep stage or adherence data.

### 4.2 Summary

The studies reviewed for this section do not negate the assumption that the FN PSG CPAP titration can be regarded as a standard. We do realize, however, that since all papers decided upon the FN PSG as the comparison standard on an a priori basis, showing that nothing else proved superior is not the same as proving FN PSG CPAP titration is a quality gold standard. The data supporting the utility of the SN PSG CPAP titration was generally of lower evidence level and usually showed feasibility rather than clear equivalence. Similar adherence, ESS, and optimal CPAP pressure in many of the SN studies supports this as an option in selected cases. The same could be said of daytime PSG CPAP although the body of evidence is much more scant. Partial PSG CPAP titration data whether attended by a technologist or not was very limited but again, portable monitoring equipment and auto-titration techniques were not evaluated for this evidence review. There was only 1 high evidence level study supporting home self-adjusted CPAP titration making this approach less easily acceptable.

### 4.3 Future Research

Although the most evidence was available for comparative assessment of split-night sleep studies, there were still too few Level I investigations to accept that future research in this area is not needed. As noted in the summary above, virtually all areas of this question require further assessment. Nearly 86% of the studies were Level IV. Although not directly reviewed in this paper, the role of portable monitoring with differing levels of sophistication may also need strong reconsideration and study to clarify many of the issues raised above.

### 5.1 On Initiating CPAP Treatment in a Patient:

#### 5.1.1 Does Immediate or Near-Immediate Initiation of Therapeutic CPAP Change Acceptance or Adherence Compared to a Delay of Days or Weeks?

There were 51 articles reviewed for this question with the vast majority meeting criteria; only 4 were excluded for a total of 47. There were 23 Level I, 14 Level II, 8 Level III, 1 Level IV, and 1 Level V studies reviewed.

One study[70] randomly imposed CPAP after PSG within 2 weeks (Group 1 -- 82 patients) or a 6 month delay for CPAP after PSG (Group 2 -- 89 patients). New patients suspected of mild-moderate (AHI = 10 to 30) or more severe (AHI > 30) OSA were then assessed for objective CPAP adherence by machine time on counter but they did this only for the group receiving more immediate CPAP (Level IV for this issue). The adherence rate in these Group 1 patients with AHI = 10 to 30 was 5.2 ± 2.1 hours per night at 3 months and somewhat less at 4.8 ± 2.3 hours per night after 6 months. In the Group 1 patients with an AHI > 30, adherence was 5.6 ± 2.0 hours per night at 3 months and 5.5 ± 2.2 hours per night after 6 months. There was no statistically significant difference in adherence between these 2 subgroups of different severity apnea but unfortunately, no adherence comparison was made between Group 1 and Group 2 patients to provide insight to our question.

No other papers specifically addressed this question and most papers did not include this issue for discussion at all. However, our committee suggested that this question could be investigated in 2 other potential ways. One approach would be to assess the impact on acceptance/adherence of the time between referral and CPAP home treatment initiation. Several papers imply that CPAP treatment is initiated sooner after a SN protocol but this did not improve adherence (see Section 4.1.2 for further details). The SN PSG and CPAP use topic was more specifically addressed in a study conducted in the United Kingdom[56] in which the median time from referral to beginning CPAP was significantly less with a SN (13 months) vs. a 2 full-night protocol (22 months). This study found no difference in the nightly CPAP time on (CPAPto) for SN vs. FN PSG groups by objective measures (6 hours vs. 6.2 hours per night); however the 1 to 2 year wait for CPAP initiation was extraordinary compared to most other studies.

Our second approach to investigate question 5.1.1 was to assess the impact of the time between diagnostic testing and/or therapeutic trial polysomnograms and the beginning of CPAP home treatment. Most papers do not specifically report the lag time between diagnostic testing and treatment initiation. One study[4]

(Level IV for single arm active CPAP data only) specifically selected patients with moderately severe apnea (AHI ≥ 30) but no daytime sleepiness (ESS < 10) and started sham or therapeutic CPAP at home the day after titration. There was no significant difference in the CPAPto for CPAP vs. sham (5 ± 0.4 vs. 4 ± 0.5 hours per night) after 6 weeks in this group of new CPAP users. This gives some indication of what to expect for adherence and compliance when CPAP treatment is initiated the day after CPAP titration PSG.

### 5.1.2 What is the Expected Acceptance and Adherence When Measured Objectively, Subjectively?

One of the best known studies for this question was a prospective investigation of CPAP adherence by Kribbs and coworkers[71] (Level I) which found that subjective and covertly monitored objective CPAP adherence were discordant and that OSA patients in aggregate overestimate subjective CPAP adherence compared with objective adherence measurements obtained by microprocessor. Adherence was arbitrarily defined as ≥ 4 hours of CPAP usage for ≥ 70% of the nights monitored. Although 60% of patients subjectively reported nightly use of CPAP for a mean of 106.9 days, only 16 of 35 (46%) were objectively using CPAP at least 4 hours per night on 70% of the nights. Patients over-estimated actual CPAP use by 69 ± 110 min. The regularity of use was determined by the first month use with an overall mean use of 66 ± 37% of the days used for mean CPAPto = 4.88 ± 1.93 hrs/night with the percentage of time that patient's were on the effective CPAP pressure (CPAPeff) = 91 ± 14.7% of the CPAPto time. They concluded that longer-term CPAP use fell far short of optimal for a large percentage of patients. A secondary analysis of the Kribbs study by Weaver, et al,[72] (Level III) also suggests that patterns of CPAP usage are manifest within the first week of therapy. Consistent users were redefined as those applying CPAP > 90% of the nights while the intermittent users skipped CPAP use 1 or more nights each week. Once patterns of usage were established after the first week, these patterns again remained stable at 1 and 3 months for the 2 groups.

There were 10 Level I papers[4,6,7,11,55,71,73-76] that addressed home CPAP use over various periods of time looking at different populations including new and established CPAP users. Objective use was reported in terms of CPAPto and/or CPAPeff. Studies describing CPAP acceptance and adherence in the context of other interventions such as mask interface type, humidification, or follow-up and education plans are discussed under Section 5.1.3. Only 1 paper[75] included both subjective and objective reports in established users. In Rauscher's group of 63 moderate OSA patients CPAP use of at least 1 year (mean = 539 ± 44 days), the CPAPto of 4.9 ± 0.3 hours per night differed notably from that reported by the patients at 6.1 ± 0.3 hours per night. Another smaller study[55] of 17 moderately severe OSA patients with established CPAP use for 820 ± 262 days showed that objective CPAPto in the first year (prior to participation in the study) was not significantly different during the subsequent study period (7.1 ± 1.1 vs. 6.9 ± 1.3 hrs/night). The third and largest study of this group[73] prospectively measured long-term objective adherence and adherence rates. Of 233 new OSA patients enrolled, 19 initially refused CPAP (8.2%) and after 874 ± 48 days, 181 patients continued (84.6%) with a CPAPto = 5.6 ± 0.1(SEM) hours per night (range 0.9-10.3 hours).

Four more Level I studies examined objective adherence rates during randomized controlled trial (RCT) studies that included a placebo tablet[6,11] or sham CPAP.[4,7] In the crossover design placebo tablet trial,[11] the CPAPto was lower at 3.7 ± 0.4 (SE) hours per night with CPAPeff at 89 ± 3% after 4 weeks of CPAP in these newly diagnosed, moderately severe OSA patients (AHI = 49 ± 1.5). Another RCT study using a placebo tablet arm revealed a low mean use of CPAP use-3.5 ± 2.1 but showed a bi-modal use pattern of CPAP with 12 patients using the device 1.7 hours per night and 11 pts using it for 5.5 hours per night while placebo use was at 93% of nights.[6]

The first active vs. sham CPAP study[7] in 60 patients with severe OSA (mean AHI near 60 in both groups) reported objective CPAPto near 5.5 hours per night in both groups. Results of the second sham CPAP study are somewhat lower as noted under section 5.1.1.[4]

Two of the remaining 3 Level I studies in new CPAP users looked only at longer-term objective CPAP use. In a study conducted by Reeves-Hoche,[76] 38 of an initially enrolled 47 severe OSA patients showed a CPAPto of 4.7 hours per night (range 0 - 10.2) and CPAP use at effective pressure was 68% of the stated sleep time. All but 5 patients (87%) in this study reported all night CPAP use. Objective measures of CPAP use (time on per hours of sleep) in these patients did not greatly change after 2 weeks of use and up to 28 weeks of follow-up. The second large study of 121 new CPAP users with severe OSA[74] noted a high CPAPeff/CPAPto ratio ranging from 94-98% throughout the study measurement points of 1, 2 and 3 months use. They were able to distinguish compliant vs. non-compliant groups of patients by using objective measurements at follow-up. The Kribbs study[71] has already been addressed above and compared both objective and subjective adherence.

There were 13 Level II papers[10,32,47,56,72,77-84] that related to this question category with only 2 papers clearly reporting both objective and subjective adherence. In 1 study[77] of 204 established CPAP users (mean 632 days, range 16 - 2921 days) self-reported CPAP use was 5.8 ± 2 hours per night. In a subgroup of 62 patients, however, objective (run-time adherence) vs. self-report of CPAP use was significantly different (p = 0.003) at 5.1 ± 2.5 vs. 6 ± 1.9 hours per night. In the only study of newly diagnosed patients with very mild apnea,[10] the overall group CPAPto and CPAPeff was not different from oral placebo although notably low at 3.2 ± 2.4 and 2.8 ± 2.1 hours per night. There was, however, a significant difference (p < 0.001) for the 24 patients in this study with both subjective CPAP data, (4.5 ± 2.5 hours) vs. objective CPAPeff (3.5 ± 2 hours). Another paper was especially difficult to interpret,[78] enrolling 33 new and established CPAP patients and randomizing to 3 different forms of follow-up. Patients were also allowed to read their own meters at 1 to 2 months reporting either CPAPeff or CPAPto (range 4.4 to 7.1 hours per night) (see 5.1.3 below). The reported objective adherence for SN vs. FN PSG is noted in response to question 5.1.1 above.[56]

Three papers[79,80,85] reported subjective adherence alone. The largest of these studies examined 300 consecutive patients[80] of unreported OSA severity established on CPAP for over 6 months. Eighty-three percent reported nightly use (mean = 7.8 ± 8.1 hours per night). In a study using a symptom questionnaire,[79] subjectively reported continued use of CPAP was 82% (79/96 respondents) in established CPAP users at 3 ± 4 months. The third study focused on new CPAP users[85]; 85% of their 96 patients with severe OSA agreed to take home CPAP initially, and 76% reported

continued use at 14.5 ± 10.7 months.

There were 6 more Level II papers[32,47,72,81-83] that described only objective measures of adherence. Three of these papers examined newly diagnosed CPAP users. The largest study of 54 patients[32] with a broad OSA severity range, reported a CPAPto = 4.7 ± 0.4 hours per night at 1 to 3 months with the CPAPeff = 89 ± 3% of CPAPto. In a different study, 39 of 44 more severe, new OSA patients[83] were still using CPAP after a mean of 9 months: Thirty-eight were regular users (97%) at CPAPeff = 5.9 ± 1.1 hours per night. During the first 9 weeks of new CPAP use in 32 more severe patients,[72] only 53% were consistent users (> 90% nights) with CPAPeff = 6.2 ± 1.2 hours per night vs. inconsistent users who had a CPAPeff of 3.5 ± 1.9 hours per night. In the 3 other studies with only objective use data, all were established CPAP users. The biggest study of 117 patients (76% of the original 155 who agreed to try CPAP at home) showed a mean adherence rate of 5 hours per night at 784 ± 366 days that did not differ from a smaller subgroup measured at 2 consecutive yearly time points.[47] In another long-term study,[81] 81% of patients agreed to take home CPAP and at a mean of 14 months (range 8-39), 68% of these 44 patients with severe OSA had a CPAPto of more than 5 hours per night. The last study[82] of 106 patients showed that between 3 and 4 months, patients used CPAP 88% of the days (range 16-100%) with CPAPto = 4.9 vs. CPAPeff = 4.5 hours per night.

A total of 5 papers met Level III criteria[86-90] with one study[87] simply stating that 63 of 103 OSA patients continued with CPAP use for 18 months to 10 years but provided no specific daily or hourly use rate. Another 2 studies[86,89] only had objective adherence data available from 12 patients. The 2 remaining studies[88,90] both reported subjective adherence rates in established CPAP users after at least 6 months at over 6.5 hours nightly use. One of these studies used group education sessions every 6 months and compared both subjective and objective use.[90] They noted the CPAPto use in 25 patients increased from 5.2 ± 0.5 hours per night at a mean of 463 ± 69 days to 6.3 ± 0.6 hours per night at a mean of 212 ± 22 days later during which time they subjectively reported the nightly use to be 6.6 ±.3 hours per night.

#### 5.1.3 What Pre-Initiation Factors Predict or Potentially Affect Acceptance or Adherence (e.g., Severity of OSA, Pressure Level, Interface Type, Having a Plan for Treatment of Side Effects, etc.)?

Thirty-four trials evaluated the outcomes of various interventions affecting CPAP adherence and side effects. The remainder of the studies were case-control or case-series designs. Acceptance and adherence issues regarding the effect of various interventions such as humidification, mask interfaces, and education or follow-up plans are reviewed here but other treatment-effect issues are discussed under Section 6.1. Studies with CPAP adherence not designated as the primary endpoint that were reviewed mainly provided documentation of CPAP-related side effects and in a number of studies measurement of specific side effect prevalence (see Section 6.1).

The influence of OSA severity or AHI level on CPAP adherence has been evaluated in 12 studies [10,32,56,73-75,81,82,85,91-93] (5 Level I, 5 Level II, 2 level III) with variable results, but the preponderance of evidence (8 positive and 4 negative impact studies) favors a positive influence of OSA severity on subsequent adherence with CPAP. An early RCT study[73] (Level I) which was the largest of this group (181 of 233 new OSA patients continued CPAP more than 2 years) reported excellent long-term objective adherence and compliance rates and hours of CPAP use did correlate with baseline AHI, but it was expected to be a positive correlation and that was not the case in this study ($r = -0.18$, $p < .02$). Popescu[92] (Level III) evaluated data derived during a 2 week home CPAP trial in 209 patients to identify factors associated with more compliant longer term use of CPAP. The 153 patients (73.2%) who accepted home CPAP had a higher baseline AHI (40.4 ± 23.4 vs. 31.8 ± 20.6, $p = 0.016$) and 1 year later, 128 (68.5% on an intention to treat analysis) continued to use the machine with a mean use of 5.0 ± 2.4 hours per night. McArdle and colleagues[56] (Level III) also examined determinants of objective CPAP use prospectively in 1,155 patients with a median follow-up of 22 months. The AHI was an independent predictor (AHI ≥ 15; $p < 0.001$) and was a significant determinant of the hours per night that the CPAP was used ($p = 0.004$). Eighty six percent of patients with ESS > 10 and an AHI ≥ 30 were still using CPAP at 3 years. Lack of benefit and side effects were the most frequent reasons for discontinuing CPAP. In another long-term study,[81] high CPAP adherence and CPAPto was associated with both higher baseline AHI ($R = 0.37$, $p = 0.013$) and the difference in AHI after treatment ($R = -0.34$, $p = 0.025$). In a study of 106 severe OSA patients by Noseda and colleagues[82] after 3 to 4 months of use showed good CPAP adherence rates (CPAPto near 5 hours per night) and a weak but insignificant correlation with baseline AHI ($R = 0.15$, $p > 0.05$). Engleman[12] (Level I) studied 16 consecutively recruited patients with mild OSA (AHI = 5 ± 14.9 and 2 or more symptoms of OSA) in a prospective RCT with 4 weeks on either placebo or CPAP. The objective CPAPto was 2.8 ± 0.7 hours per night and 10 of 16 patients preferred CPAP (i.e., opting to continue treatment) but this proportion was non-significant vs. the placebo CPAP group ($p > 0.4$). Those who complied better with CPAP therapy did have a higher average AHI ($p = 0.02$) than the poorer compliers. In the study[93] (Level I) with 38 of 47 patients agreeing to use CPAP for severe apnea, the CPAPto was higher than the preceding study at 4.7 hours per night and although the baseline AHI did not correlate with CPAPto adherence, a high AHI did correlate with CPAPeff use ($R = 0.27048$, $p = 0.0006$). Similarly[75] (Level I) in 63 established CPAP users after 1 year, severity of baseline AHI level distinguished patients who objectively used CPAP for > 4 hours per night vs. those using CPAP < 1.5 hours per night ($p = 0.049$), although higher AHI levels did not identify patients using CPAPto more or less than 80% of reported sleep time.

There were 4 negative studies beginning with Engleman[10] (Level II) who in 1 of the later studies reported no correlation between AHI and CPAP adherence in a larger RCT. Thirty-four patients with mild AHI (5 to 15) and daytime sleepiness spent 4 weeks on each treatment arm. CPAP use was much lower than other studies and AHI showed no significant regression with treatment effects. The lack of correlation between adherence and AHI was also noted in 1 of their studies described earlier[32] (Level II). In another study randomizing patients to having a covert CPAP use monitor or not as discussed earlier[74] (Level I), the authors reported generally good adherence over the first 3 months of CPAP use but they did not find any correlation with CPAPto and AHI at baseline or after CPAP initiation. Lastly, as noted above under section 4.1, a study that reviewed 125 OSA patients[85] (Level II), revealed there were no statistically significant differences between the compliant and noncompliant patients in baseline AHI. They concluded that compliant and noncompliant patients who

have equally severe sleep apnea could have a good initial response to nasal CPAP.

The effect of the necessary CPAP pressure level on CPAP adherence has also been evaluated in 7 studies[4,7,17,71,87,93,94] (5 Level I and 1 level III) but most authors make only vague reference or supply limited details relevant to this issue. The data suggests there is little to no dependence of CPAP pressure level on subsequent adherence. Mixed results were reported in 4 trials comparing therapeutic vs. sub-therapeutic or sham CPAP treatment levels. The first of the 2 parallel RCT trials[17] (Level I) of therapeutic vs. sham CPAP was done in 107 men with OSA and sleepiness. CPAP adherence was 5.4 hours per night (therapeutic) and 4.6 hours per night (subtherapeutic) with therapeutic being superior to subtherapeutic CPAP in all primary outcome measures. The use of CPAP by the therapeutic group was 48 minutes per night longer than that of the subtherapeutic group ($p = 0.035$). Another parallel RCT study[94] (Level I) also compared nasal CPAP set at therapeutic or subtherapeutic levels of pressure after 1 month in 101 men who had OSA and were sleepy. All outcome measures also improved significantly in the therapeutic group, compared to the subtherapeutic group.

The third RCT study that included a sham CPAP arm[7] evaluated 60 consecutive patients with moderate to severe OSA who were randomly assigned to either effective or subtherapeutic nasal CPAP for 9 weeks on average. Although apneas and hypopneas were reduced by approximately 95% vs. 50% in the therapeutic vs. subtherapeutic groups, respectively there was no difference in adherence. The final study comparing therapeutic and sham CPAP[4] (Level I), as described earlier in section 5.1.1, also showed there was no difference in CPAP adherence after 6 weeks. These patients with moderate apnea were also specifically selected so as not to have any daytime sleepiness or other major OSA symptoms.

Three other studies[71,87,93] (2 Level I and 1 Level III) assessed effect of CPAP pressure level on CPAP adherence. The first of these studies[87] (Level III) characterized patients who were either able or unable to tolerate CPAP treatment (non-complaint vs. complaint). The patients who continued CPAP actually had slightly but significantly higher CPAP level requirements ($p < 0.01$), perhaps reflecting a more adequate therapeutic titration. The Kribbs[71] (Level I) study detailed in several sections above found no difference in CPAP pressure requirements between regular and irregular CPAP users. The last study[93] also showed no difference between the degree of prescribed CPAP pressure and adherence.

There were 4 Level I studies[95-98] that utilized an RCT, crossover or parallel design and there was 1 Level IV study[99] which compared different nasal, oral, or full-face masks. A parallel RCT study[95] was performed with full-face vs. nasal mask CPAP therapy for 4 weeks in 20 OSA patients with or without previous uvulopalatopharyngoplasty (UPPP). Nightly CPAPto adherence after 1 year was higher with a nasal vs. full-face mask ($5.3 \pm 0.4$ vs. $4.3 \pm 0.5$ hours per night, $p = 0.01$) for OSA patients but in patients with previous UPPP and OSA, adherence was only marginally higher with nasal vs. full-face masks (CPAPto = $5.1 \pm 0.7$ vs. $4 \pm 0.8$ hours per night, $p = 0.07$). During this RCT trial showing better adherence with the nasal vs. full-face mask, nasal masks were rated more comfortable by 19 of 20 patients ($p < 0.001$) despite more mouth leak related symptoms. The authors concluded that adherence is greater with a nasal vs. full-face mask because the overall comfort is better and compensates for increased symptoms associated with mouth leakage. The Level IV study[99] that also studied full-face CPAP mask in 10 males who could not tolerate nasal CPAP due to nasal congestion compared the effects of a therapeutic level of CPAP pressure applied through a nasal or full-face mask in patients with moderate-severe OSA. The AHI response (reduced to < 8 events hour) on CPAP nights were similar regardless of mask type so the authors concluded that the full-face mask may be a reasonable treatment alternative in patients who cannot tolerate nasal CPAP but they did not assess CPAP adherence rate.

In 1 of 2 studies[97] comparing a nasal vs. oral mask (Oracle mask, Fisher-Paykel, Auckland, NZ) was done in 21 newly diagnosed severe OSA patients (mean AHI = 85 per hour) for 4 weeks and found there was no significant difference on objective CPAP adherence CPAPto and % pts using at least 3 hours per night. Their values however were notably low compared to other studies (nasal vs. oral CPAPto = 3.8 vs. 3.5 hours night; percentage of patients using 3 hours per night = 62 vs. 57%). Another nasal vs. Oracle mask study[98] with a parallel RCT design of 38 patients with severe OSA (mean oral vs. nasal RDI = 58.5 vs. 63 per hour) reported objective and subjective adherence rates at 1 and 2 month follow-up. There was no significant difference for either mask at either follow-up periods for objective average hours per night [oral vs. nasal month 1 and month 2 CPAPto (with percentage of patients using 4 hours per night) = $4.6 \pm 2.1$ (52%) vs. $4.3 \pm 2.6$ (47%) at 1 month and $5.5 \pm 2.6$ (73%) vs. $4.6 \pm 2.5$ (67%) at 2 months]. Twenty-nine percent of patients in each group dropped out by 2 months. The subjectively reported average hours per night tended to be somewhat higher than objective reports (subjective oral vs. nasal month 1 and month 2 CPAP time = $5.8 \pm 1.4$ vs. $5.8 \pm 1.7$ at 1 month and $5.8 \pm 1.7$ vs. $5.7 \pm 2.6$ at 2 months).

In the last interface study, an RCT crossover trial[96] was done on 39 new patients with OSA comparing nasal pillows (Breeze; Mallinckrodt Corporation; Minneapolis, MN) and a nasal mask (Contour; Respironics; Murrysville, PA) after a 3-week treatment period. The percentage of days CPAP was utilized favored the nasal pillows (94.1% vs. 85.7%; $p = 0.02$), but nightly minutes of use were similar (nasal pillows, 223 min; nasal mask, 288 min). Fewer adverse effects, less sleep difficulty and air leak occurred with nasal pillows ($p < 0.04$). The authors concluded that nasal pillows were associated with fewer adverse effects and better sleep quality.

Six studies[83,100-104] are published evaluating the use of humidification to augment CPAP adherence and also evaluated other interventions effects. As noted earlier, Massie et al,[100] (Level I) found that a heated humidifier increased adherence compared to either room temperature humidifiers or no humidification and specific side effects such as dry mouth or throat and dry nose were reported less frequently when CPAP was used with heated humidity compared to CPAP use without humidity ($p < 0.001$). Subjective patient satisfaction with treatment was equally improved for heated or room temperature humidifiers compared to no humidification. A similar study by Neill, et al,[101] (Level I) demonstrated a small improvement in adherence with heated humidification, but no difference in subjective sleepiness or treatment satisfaction. A Level II study[104] examined initial preferences in new CPAP users over 2 consecutive nights either with or without humidification. They concluded that the use of humidity during the initiation phase of CPAP treatment was associated neither with an initial improve-

ment in comfort nor with greater initial treatment acceptance.

Three lower evidence level studies[83,102,103] have also evaluated heated humidification use with CPAP. One study[102] (Level III) of 24 OSA patients complaining of serious CPAP-related upper airway dryness were randomized to 6 weeks of either heated humidification or oily nose drops demonstrated that heated humidification was more effective than non-heated humidification in increasing measured absolute humidity. No patient that received heated humidification discontinued CPAP therapy but only 5 of 12 patients (42%) in the oily nose drops group reported their degree of upper airway dryness to be improved (P =0.003) while all 3 of the patients who intended to terminate CPAP did so. A second study[103] (Level III) evaluated how nasal CPAP therapy influences the relative humidity (rH) of inspired air; and how the addition of a heated humidifier or a full-face mask may effect the rH in 25 OSA patients receiving long-term nasal CPAP therapy and complaining of nasal discomfort. When comparing the values obtained with CPAP alone, heated humidification significantly increased rH during the sleep recording, both when the mouth was closed and during mouth leaks but they did not assess the effect on humidity on CPAP adherence. A retrospective, case-series design study[83] (Level V) looked at the effects of CPAP on infectious complications by analyzing the kinds and rate of infections of the upper airway in 246 consecutive patients with or without a heated humidifier and compared them with OSA patients who did not receive CPAP therapy. Forty patients received conservative therapy and 206 CPAP treatments, 36 of them with a heated humidifier with a mean follow-up of 165.4 ± 92.1 weeks. Patients using CPAP without the humidifier had significantly more upper airway infections than controls (42.9 vs. 25%; $p < 0.05$), and more patients on CPAP therapy with humidifier than controls (22.2 vs. 2.5%; $p < 0.01$) reported an increased rate of upper airway infections since initiation of CPAP therapy or diagnosis of OSAS. Patients who did not adequately clean their heated humidifier devices had significantly more upper airway infections since diagnosis (57.1 vs. 20%; $p < 0.05$) or during the past 6 months (52.4 vs. 13.3%; $p < 0.05$) than patients who regularly cleaned CPAP machines, humidifiers and ventilatory circuits. They concluded that humidification, especially if daily cleaning of the humidifier is not facilitated, is an increased risk of infection but the effect of this on adherence was not assessed.

Six studies, all prospective, (4 Level I,[91,105-107] and 1 each, Level II,[78] and Level III[88]) have evaluated the impact of enhanced patient education programs on CPAP adherence. Three out of the 4 studies found that increased intensity of patient education or frequency of health provider contact resulted in improved adherence rates. Chervin, et al,[78] found that additional printed patient education materials or weekly health provider telephone calls increased adherence compared to the control group. Another RCT study[105] of 80 new CPAP patients on more intensive vs. standard follow-up reported a significant difference for each group in time at effective CPAP level of 5.4 hours per night vs. 3.8 hours per night at 6-month follow-up. Hoy et al,[105] combined 3 nights of initial observation in a sleep laboratory with weekly home visits from a nurse, with a resultant increase in mean usage from 3.8 hours per night to 5.4 hours per night after 6 months ($p = 0.003$). This intensive approach to promoting CPAP adherence increased hours of nightly CPAP usage at 1 and 3 months of CPAP treatment. Patient reported CPAPto in the Palmer study was assessed serially and baseline and 3 months after randomization to either nurse home visits or office consultant review.[107] The study was conducted in 139 long-term established CPAP users of unknown OSA severity (AHI not provided) whose baseline nurse vs. consultant CPAPto of 4.9 vs. 5.2 hours per night increased significantly ($p < 0.04$) in both groups to 5.9 vs. 5.6 hours per night but there was no difference related to the follow-up person. In contrast to the other 5 studies, Hui et al,[106] found no change in CPAP adherence with weekly phone calls from a nurse but did demonstrate improved quality of life for patients attempting to use CPAP.

A very recent study[91](Level I) assessed the impact of a computer-based telephone system (TLC) designed to improve initial CPAP adherence compared to usual care in patients with moderately severe OSA (mean AHI near 40). TLC is a computer-based system that provides structured education and reinforcement for CPAP use. New CPAP users were enrolled and at the 2-month follow-up, CPAPeff for the TLC group was significantly different at 4.4 hours per night compared with 2.9 hrs in the usual care group and there was a more significant ($p = 0.047$) reduction in the sleep symptom scores for the TLC group. They did not report the lag time between diagnosis and initiation of CPAP therapy or the difference in adherence between the 2 subgroups of different apnea severity.

The second Level I augmented education/follow-up RCT study[106] reported both objective and subjective adherence rates in 108 new patients with moderate-severe OSA (AHI = 48) at 4 and 12 weeks follow-up. There was no significant difference in objective CPAPto at both follow-up periods for both the basic and augmented support groups at all time periods averaging 6.3-6.5 hours per night with over 70% of patients using CPAP ≥ 4 hours per night for at least 70% of the nights of the week.

### 6.1 Once CPAP Treatment Has Been Initiated and Excluding Acceptance and Adherence Issues From Question 3, How and How Often are the Following Documented to Determine Efficacy, Effectiveness and Safety?

The literature search identified 497 studies that met the extraction criteria for this question. After an initial review excluding studies with only peripheral relevance to this body of literature, 64 studies were fully extracted and referenced in the evidence tables. There were 17 Level I, 7 Level II, 14 Level III, 15 Level IV, and 11 Level V studies utilized. Case studies and articles related to comments are not included in the evidence table but are referenced.

#### 6.1.1 Adequacy of CPAP Treatment Including Pressure Settings and Interface Type

The occurrence of patient complaints related to pressure intolerance or interface problems are the most commonly reported CPAP-related side effects (See section 6.1.3). As CPAP usage patterns are established very early after the initiation of treatment, pressure or interface related side effects are often promptly addressed ([92] Level III,[108] Level IV). Recommendations for longer-term provider follow-up are not certain, but equipment obsolescence, including mask, headgear, tubing and other items suggest yearly health care provider follow-up reasonable as a method choice for many studies. The need for serial adjustment of CPAP settings in the clinical setting is not known, but studies do suggest that initial laboratory specified pressures are usually a few cm $H_2O$ higher than that specified on repeat titration study a few

weeks later (see details below). The use of APAP is not included in this review. In addition, the possible use of bilevel PAP to address pressure intolerance is addressed in Section 7.1. The need for repeat or serial long-term (for example, every year) CPAP titration studies was not well supported, although logic encourages recheck for persistent adherence problems or the recurrence of symptoms of untreated OSA.

Three studies revealed that discontinuation of CPAP either 1 night ([109,110] Level III) or even half of the night ([111] Level V) resulted in the recurrence of obstructive respiratory events and the clinical sequelae of untreated OSA including hypersomnia. Despite adherence with therapy, OSA usually persists with unchanged severity over 2 years after diagnosis ([110] Level III). However, pressure requirements vary with time and other studies suggested that CPAP level is decreased approximately 2 cm within 2 to 4 weeks of initiating treatment ([18] Level II). Initial titration in the sleep lab was higher based on a 2-month interval evaluation. Bureau showed that subsequent downward titration of CPAP with introduction of CPAP during PSG can reduce the optimal CPAP recommendation ([40] Level IV).

No studies were found to determine whether a fixed CPAP level specified soon after diagnosis was adequate after 3 months or longer after the start of treatment. There have been no studies demonstrating the need for routine, serial CPAP titration studies such as on an annual or bi-annual basis. Specifically, no study has directly evaluated whether an initially adequate CPAP level might result in an elevated AHI at a later time but it is known that the prevalence of OSA increases with aging.[112]

In the face of significant weight loss, CPAP pressure levels may need to be adjusted. Obesity is a well-recognized risk factor for the occurrence of OSA and studies have shown that the severity of OSA is reduced in many patients who lose weight. In fact, the need for CPAP treatment may be negated for some patients with weight loss.[113] Changes in CPAP level requirements with serial titration studies at various weights for individual OSA patients have been cited in case reports and case-series with small numbers (fewer than 10 subjects) such that these were not included in this literature review. No larger studies have evaluated the pressure requirement over time with changes in weight.

Four studies evaluated the use of humidification to augment CPAP adherence. Massie et al,[100] (Level I) determined that a heated humidifier increased objectively measured adherence compared to either room temperature humidifiers or no humidification. However, subjective patient satisfaction with treatment was equally better for heated or room temperature humidifiers compared to no humidification. A similar study by Neill, et al,[101] (Level I) demonstrated a small improvement in adherence with heated humidification, but no difference in subjective sleepiness or treatment satisfaction. Two lower evidence level studies have also evaluated heated humidification use with CPAP. A study by Martins de Araujo et al[103] (Level III) demonstrated the effectiveness of heated humidification in decreasing nasal discomfort even in the face of persistent mouth leak. However, a retrospective, case-series design study ([83]Level V) suggested an association between CPAP use and upper respiratory infections which is compounded by the use of heated humidification, especially if daily cleaning of the humidifier is not facilitated.

Several controlled studies are available addressing the advantages or disadvantages of specific interfaces for CPAP as a primary endpoint. Described interfaces include nasal masks, oronasal masks, nasal prongs, and oral only masks. Mask fit and comfort, as well as the presence or absence of mask leak and mouth leak, are specific issues that are assessed in the studies evaluating CPAP side effects as discussed below. During the RCT trial showing better adherence with the nasal vs. full-face masks ([95] Level I), nasal masks were rated more comfortable by 19 of 20 patients ($p < 0.001$) despite more mouth leak related symptoms. This study determined that pressure requirements are higher for patients using oronasal CPAP masks. One study of nasal versus a novel oral interface found no difference in CPAP adherence at up to 2 months follow-up with equivalent CPAP pressures ([97] Level I). Massie et al found improved adherence and fewer overall adverse effects ($p < 0.001$) with nasal prongs vs. one type of nasal interface but the pressure requirements were the same ([96] Level I).

No studies evaluated the impact of a ramp mechanism used with the initiation of CPAP on adherence or side effects. This mechanism is intended to facilitate a gradual increase in pressure over time during the initiation of sleep. One case report cites repeated patient activation of the ramp feature which led to marked recurrence of apneas and hypopneas.[114]

### 6.1.2 Treatment Effect Such as Continued Reduction in AHI or Respiratory events, Improvement in Sleepiness, Psychological Benefit and Quality of Life, or Systemic Blood Pressure

The discussion for Section 3.1 provides a comprehensive review of the physiologic and performance-based outcomes that occur with effective CPAP treatment. A preponderance of evidence demonstrates the resolution of the nocturnal respiratory events with standardized methods of CPAP titration. Section 6.1.1 noted the reoccurrence of disordered breathing with abrupt withdrawal of CPAP[109-111] as well as the persistence of AHI elevation even after 2 years of CPAP use so there is no clear evidence of a treatment effect on baseline AHI or other respiratory events.

A recent literature review on the clinical indications of the MSLT[115] included many studies assessing the utility of this test in assessing response to CPAP treatment in OSA. The majority of these studies demonstrated an increase in the mean sleep latency with CPAP treatment. However, one should note that both pretreatment and post-treatment means were within 1 standard deviation of normal control means. There were 13 studies reporting MSLT results cited in the evidence table for this section with 5 Level I studies showing a positive effect from CPAP[11-13,17,116] and 1 of these studies showed the CPAP benefit after 4 weeks with mean use of < 4 hours per night[11]. Two studies showed no change in the MSLT with CPAP use between 2 weeks and 4 months.[18,28] Two more reports noted no difference on the MSLT when comparing intensive follow-up to routine care ([78]Level V, [105] Level I). Three lower evidence level studies also supported a significant improvement in the MSLT with CPAP treatment of 24 hours[117] to 6 months or more ([118] Level III, [119] Level IV). Two other lower evidence level studies showed a relation between adherence rate and MSLT benefit ([89] Level IV, [109] Level III) and 1 of these demonstrated that the MSLT change was sensitive to even a 1 day withdrawal of CPAP treatment.[109] None of these investigations revealed a direct impact of the MSLT changes on the management of CPAP pressure adjustment or need for reassessment.

As discussed in question one, the Epworth Sleepiness Scale (ESS) has been evaluated as an indicator for OSA severity and

used in clinical settings to assess treatment response.[120] There were 23 studies reviewed for this section that utilized the ESS or some other measure of subjective sleepiness to assess CPAP response (13 Level I, 1 Level II, 4 Level III, and 5 Level IV). A poor correlation between ESS, pre-treatment AHI and measured mean sleep latency has been reported ([78] Level II). The ESS value also did not show an effect from humidity ([100] Level I), relationship with adherence or age ([121] Level III) or with more intensive follow-up ([105,106] both Level I). Two more studies did not show any effect of CPAP treatment on the ESS after either 1 week ([18] Level I) or up to 2 months of treatment ([7] Level I). The preponderance of studies however did show improvement in the ESS with CPAP treatment (9 Level I[13,17,28,81,97,101,122-124]; 2 Level III,[83,86] and 5 Level IV[81,119,125-127]). Two of the Level I studies reported improved ESS scores at 4 weeks with less the 4 hours per night adherence[13,97] and 2 other studies stated either nasal prongs[96] or a full-face mask[95] showed a positive effect on the ESS.

Sleepiness from all causes, especially OSA, is well known to negatively affect driving performance. In OSA patients (untreated or with increasing OSA severity as measured by AHI), 3 of 4 studies ([125] Level IV, [72] Level II, [127] Level IV) have shown a positive effect on reduction in motor vehicle accident rates. Kribbs, et al[71] (Level I) did not find an increase in self-reported, sleepiness related near-miss motor vehicle accidents associated with decreased, objectively measured CPAP use. However, re-analysis of these data[72] did demonstrate that consistent CPAP users reported fewer accidents than intermittent users. The Level IV studies[125,127] showed reduced self-reported driving accident rates with initiation of CPAP and a relationship with severity of OSA. Self-reported motor vehicle accidents may not be an accurate end-point due to the potential for its under-reporting in non-compliant CPAP patients who could be legally liable when an accident occurs.

A positive effect with CPAP treatment on objective driving performance tests was demonstrated in 4 of 5 studies ([11] Level I, [128] Level III, [119] Level IV, [129] Level III, [130] Level IV). CPAP treatment in a high evidence level study improved driving performance measured by a simulator after only 4 weeks of treatment ([11] Level I). Although daytime sleepiness decreased with improvement of other vigilance tests, driving simulation by 'steer-clear' testing did not change with CPAP up to 12 months later in one lower evidence level study.[130]

The Functional Outcomes Sleep Questionnaire (FOSQ) is a self-administered survey which evaluates the impact of sleepiness on the ability to perform activities of daily living ([72] Level II). The FOSQ score improves with CPAP treatment after 6 weeks compared to sham CPAP([25]- Level I) and up to 6 months ([105] also Level I) but it was not sensitive in confirming the advantage seen by other parameters for nasal prongs over a conventional CPAP mask.[96] The concordance between continued, objectively measured CPAP use or other parameters and the FOSQ has not been evaluated over longer time intervals.

In the study that randomly imposed immediate CPAP after PSG within 2 weeks or a 6 month delay[70] for PSG and CPAP, the primary objective was to look at the effect of delayed treatment on daytime sleepiness, cognitive function, and healthcare expenditures. Many studies have included quality of life, performance, and mood measures before and after treatment with CPAP. In untreated severe OSA patients, quality of life was often assessed with the Medical Outcomes Study Short Form 36 (SF-36) with several high evidence level studies ([17,25,96]- Level I; [131]- Level III; [119]- Level IV). At baseline, SF-36 was decreased in a number of domains and all studies showed general improvement with CPAP.

The relationship between quality of life, mood or depression, cognition and other neuropsychiatric variables in patients with obstructive sleep apnea syndrome has also been assessed with a wide variety of investigative tools. There were 17 additional studies beyond those utilizing the SF-36 that investigated these areas ([11-13,18,28,70,101,105,106] Level I; [21,132] Level II; [122,131] Level III; [119,126,130] Level IV, [133] Level V). Although the vast majority of studies showed improvement with selected testing after CPAP, several did not. One Level III investigation[122] demonstrated that although most neuropsychiatric deficits normalized with treatment, planning abilities and manual dexterity did not normalize after 6 months of CPAP use. The authors speculated that since the latter parameters have been found to highly correlate with the severity of nocturnal hypoxemia, patients with more severe apnea may have irreversible deficits. Two Level I studies found either that CPAP improved both objective and subjective sleepiness, but not psychometric parameters after 4 weeks,[13] or that there was no improvement in daytime function at just 2 weeks of CPAP use.[18] Slight but positive benefit was seen in cognitive tests but not in neuropsychiatric tests ([21] Level II) after 3 and 12 months, but memory and concentration tests were not sensitive in showing the benefit of humidification with CPAP use.[101] Pelletier-Fleury[70] revealed that delayed initial use of CPAP also did not change cognition despite benefits seen in quality of life. The selection of testing technique, degree of standardization, and the characteristics of the baseline population as well as the intervention must be considered since all these issues can have an effect on the findings of individual studies.

Section 3.1 addresses the immediate and shorter term impact of CPAP on systemic hypertension; 6 of the studies are included for our discussion here ([7] Level I; [134] Level II; [135,136] Level IV; [137,138] Level V). Although treatment with CPAP does decrease day and/or night blood pressure after variable treatment times, the treatment effect may be relatively modest and it is often the case that therapy with antihypertensive medication must be continued. However, Becker et al[7] found significant improvement in mean arterial blood pressure both day and night with effective CPAP (95% reduction in AHI) vs. subtherapeutic CPAP (50% reduction in AHI). Another higher evidence level study[134] demonstrated a decrease in day and nighttime blood pressure after only 3 nights of CPAP with restoration of the expected circadian effect with a nighttime 'dip' in blood pressure. Two studies showed a predominant effect on diastolic pressure after only 2 weeks[135] or at 12 - 14 weeks[136] of CPAP use. Two final lowest evidence level studies showed either a day and night blood pressure reduction only in compliant CPAP users at 8 weeks or a positive response in as little as 8 days. Labile hypertension is well described in "case-series" design studies in untreated OSA, but very few studies have evaluated this as a definite marker for non-adherence with CPAP therapy.

### 6.1.3 Adverse Events Including Equipment Failure, Interface Problems and Other Side Effects or Complications From CPAP Usage

Early adherence monitoring seems critical as the literature suggests many side effects can occur during the first few weeks of CPAP use and may lead to discontinuation of treatment.[92,108] Possible side effects are listed in Table 3. Overall, there were 24 stud-

ies entered into the evidence table for specifically commenting on complications or side effects. These were comprised of both higher and lower evidence levels (7 Level I studies- [25,28,96,97,100,101,105]; 3 Level II- [72,85,139]; 4 Level III- [71,92,103,140]; 4 Level IV- [74,81,99,108]; and 6 Level V- [79,80,83,141-143]). Less bothersome side effects may persist long-term (up to 2 years) but are less likely to impact on adherence[108,141]; however, decreased adherence or complete refusal did correlate with more side effects.[72,81,85,108,143] Studies designed with frequent patient interactions suggest > 70% adherence after 6 months despite persistence of side effects for many patients.[80,105]

Many studies evaluating CPAP treatment side effects as a primary endpoint are retrospective in design. Several lower evidence level studies reported CPAP side effects as secondary endpoints with general descriptions or lists of these side effects[71,79,80,142] but were relatively consistent and dominated by upper airway symptoms. The percentages of OSA patients experiencing various side effects are contained in a number of these prospective studies.[71,79,85]

Early retrospective studies suggested CPAP side effects occurred in > 50% of OSA patients and were persistent even for compliant patients.[74,108] Airway dryness was the most frequent complaint (> 40%[139,141]) for studies that were completed prior to the availability of humidification systems. Nasal interface side effects were noted to occur in > 50% of all CPAP patients in a number of studies and included skin abrasion, and mask leak.[74,79,139,142,144] More recent studies suggest similar frequencies of CPAP side effects within the first few weeks of treatment, but the development and application of airway humidifiers, and a multitude of nasal and oronasal interfaces may have led to increased longer term adherence rates.[96,99-101,103] Unfortunately, there are no studies showing benefit when comparing adherence rates serially in groups of newly treated patients from the same clinic or study population before and after implementation of some of these improvements. During a nasal vs. oronasal mask trial,[97] there was more nasal congestion or dryness and air leaks with the nasal mask and more oral dryness and gum pain with the oral mask, but these issues had no impact on adherence or other aspects of CPAP treatment. There was no significant difference in CPAP pressure, side effect scores, or mask preferences during this crossover study.

**Table 3**—Possible CPAP-Related Side Effects

**Interface**
Mask leak[103]
Skin abrasion/ulceration (pain)[74]
Mask allergy[80]
Conjunctivitis/Sore eyes[85,108,139]
Dermatitis/facial irritation[71,81]
Claustrophobia[71]

**Pressure-Related (Airway)**
Rhinitis[139,142]
Rhinorrhea[141]
Sneezing[141]
Desiccation[139]
Sinusitis[80]
Headache[139]
Epistaxis[28]
Otitis/Ear pain[79,141]
Air swallowing/Aspiration[142]
Belching[85]

**Pressure-Related**
Mouth leak (dry mouth) or mask leak[139,142]
Pressure intolerance[142]
Sense of suffocation or difficulty exhaling[142]
Tinnitus[108]
Aerophagia[142]
Pneumoencephalus[166]
Central sleep apnea[167]
Prolonged oxyhemoglobin desaturations[167]

**Equipment Related**
Noise[81]
Smell[79]
Tubing condensation[83]
Cumbersome equipment[108]
Spousal intolerance/less intimacy[133]
Ramp abuse[114]
Equipment maintenance and cleaning[83]

**Equipment Failure[105]**
Lifespan of machine, tubing and mask
Recurrence of OSA

**General**
Periodic limb movements[140]
Anxiety[105,108]
Insomnia[79,108]
Headache[108]
Fatigue/Feeling tired[143]
Chest discomfort[85]

### 6.2 Summary

The frequency with which efficacy and safety of CPAP needs to be assessed is not specifically clear but benefit and adherence appears to be determined within the first few weeks of treatment. Available evidence does not direct the need or timing for serial repeat titration studies and does not show a strong effect of CPAP pressure settings. Although there is clear support that CPAP resolves most respiratory events and improves sleepiness, there was no evidence for a continued change over time and resolution of the underlying disorder without the use of CPAP. The resolution of sleepiness was coupled with improved driving performance and the majority of studies revealed a positive benefit on psychometric or vigilance, neurobehavioral, and quality of life measures. However, the large variation in testing methods, population selection, and interventions made it difficult to form firm conclusions. The effect of CPAP on blood pressure appears to be variably significant during the nighttime or daytime and on systolic versus diastolic readings. Other cardiovascular parameters were not assessed in this review. Finally, there were a myriad of reported side effects and complications of treatment with some impact seen from the use of humidification and different interfaces.

### 6.3 Future Research

The utility of continuously monitoring the multitude of effects with CPAP usage is unknown. Research might best focus on more precise description of the patient population and selection techniques as well as an attempt to standardize testing techniques. Clarification of high impact interventions for the most prominent adverse events would also seem worthwhile. Certainly, the persistence or recurrence of the complaint of drowsiness while driving in OSA patients requires additional clinical evaluation and inter-

vention. Widely applicable methods to monitor and detect OSA patients at particularly increased risk for driving accidents are yet to be established. A more in-depth assessment of other cardiovascular responses such as arrhythmia and cardiac function after PAP treatment would be valuable. Lastly, continued efforts to design and assess new interfaces and PAP delivery modes should be strongly supported.

### 7. 1 Bilevel Positive Airway Pressure

Bilevel PAP may be used as an alternative therapy to CPAP in OSA or may be used to treat nocturnal breathing disorders other than OSA. Only 88 of 752 articles cited by the PAP search criteria in the years 1991-2003 addressed the use of bilevel PAP. Often, studies of bilevel PAP in OSA include patients with coexisting respiratory conditions. Four studies[76,145-147] addressed the use of bilevel PAP in patients who have OSA without comorbid respiratory conditions such as daytime hypercapnia or restrictive or obstructive lung disease.

The limited number and variable design of studies employing bilevel PAP required a modification of the criteria for accepting studies for clinical evidence grading. Studies employing bilevel PAP for nocturnal breathing disorders other that OSA often used a sample size of less than 10, failed to use a sham positive pressure treatment group, and frequently identified outcome measures such as awake or sleeping gas exchange rather than polysomnographic sleep parameters. Limiting evidence grading to studies employing polysomnography or studies with ≥ 10 subjects would have eliminated many of the 88 articles reviewed. On the other hand, including studies of negative pressure ventilation, volume cycle ventilation, or those study designs documenting only the immediate awake responses to bilevel PAP is beyond the scope the question being addressed. In order to allow a sufficient number of studies for review and yet ensure some consistency of study design, the following inclusion criteria for evidence grading were used: a) ≥ 5 subjects, b) any of 4 outcome measures (preference or use of PAP, sleep parameters, measures of daytime sleepiness, or measures of gas exchange), and c) use of bilevel PAP during sleep periods. Polysomnography was not a requirement for evidence grading. Of 88 studies using bilevel PAP, 18[76,84,145-160] met these criteria for evidence grading, 6 studies[76,147,149,152-154] employed a randomized controlled trial design and 4 used sham PAP in the control arm.[76,147,149,152] Each of these 18 articles was evaluated using the evidence grading listed in Table 1.

### 7.2 When Should Bilevel PAP Be Used Instead of CPAP in OSA Patients?

#### 7.2.1 Adherence, Comfort, and Preference.

Improvement in patient adherence to the use of PAP or improvement in mask comfort is a potential benefit of bilevel PAP in OSA patients. Two Level I studies[76,147] of bilevel PAP vs. CPAP for OSA patients without coexisting daytime respiratory disease demonstrated no difference in effectiveness or long term adherence with CPAP. In 1 of these Level I studies, adherence as measured either by the average hours that CPAP was used per night or the time during which pressure was applied per night was not different with bilevel PAP as compared to CPAP.[76] In this study, patients related no difference in complaints in the rate of mask discomfort or nasal symptoms between CPAP and bilevel PAP. The second Level I study of OSA patients without coexisting daytime respiratory disease demonstrated no difference in the percentage of nights with at least 4 hours of use between bilevel PAP and CPAP.[147] There are no Level I studies comparing adherence of CPAP and bilevel PAP in OSA patients with coexisting disease and limited evidence for patient preference in this population. Two Level III studies suggest a subset of patients with OSA and comorbidity prefer bilevel PAP as compared to CPAP.[157,159] In these Level III studies, patients with OSA who preferred bilevel PAP were more obese and had more resting hypercapnia and arterial desaturation during the day[157,159] or demonstrated more spirometric evidence of airflow obstruction as measured by FeV1/VC.[157]

#### 7.2.2 Efficacy

The 2 Level I studies comparing CPAP and bilevel PAP in OSA patients without coexisting daytime respiratory disease demonstrated no difference in the improvement in RDI with PAP.[76,147] Subjective assessment of sleepiness (ESS) and sleep quality (FOSQ) were not different with CPAP as compared bilevel PAP in 1 of these studies.[147] Similarly, 2 Level III studies demonstrated no difference in RDI between CPAP and bilevel PAP in OSA patients with coexisting COPD, obesity, or hypoventilation.[145,157] In 1 Level III study of OSA patients who exhibited a nocturnal rise in $PCO_2$ of > 19 mmHg, subjective reports of morning headaches, insomnia, and daytime hypersomnolence resolved with bilevel PAP.[146] There was no comparison to the effect of CPAP in this study.

#### 7.3.1 What are the Indications for Bilevel PAP Treatment of Nocturnal Breathing Disorders in Other than OSA Patients?

Eleven studies have examined the effect of bilevel PAP in patients with obstructive and restrictive lung disease[84,148-151,153-156,158,160] with the intent to support ventilation rather than to improve RDI. Because treatment studies have been targeted to these specific categories of lung disease and because of the limited number of studies and the heterogeneity of chosen primary endpoints, the discussion will focus on outcome measures according to disease category.

#### 7.3.2 Efficacy of Bilevel PAP in COPD Patients.

The most persuasive precedent for using bilevel PAP in breathing disorders derives from 7 randomized controlled trials in the setting of acute respiratory failure complicating COPD.[161] These studies often employed relatively high initial inspiratory pressures (15 - 20 cm $H_20$) that were based on a preliminary study demonstrating improvement in objective measures of respiratory distress and gas exchange in COPD patients with acute respiratory failure.[162] Higher ventilatory pressures might be required in COPD as compared to neuromuscular disease because of the higher respiratory impedance in COPD. Though the studies of bilevel PAP in COPD patients with acute respiratory failure show a reduction in mortality rate and a reduction in the need for invasive ventilatory support,[161] the role of bilevel PAP as therapy during sleep in chronic respiratory failure is less defined. Theoretical benefits from nocturnal ventilatory support might include improvements in awake and sleeping gas exchange due to increased sleeping ventilation, deeper and less interrupted sleep, and in-

creased awake respiratory muscle strength after resting fatigued respiratory muscles during sleep.

Four Level II studies[149,152-154] have addressed the use of bilevel PAP during sleep in clinically-stable hypercapnic COPD patients ($PCO_2$ > 44 or 45 mmHg). These studies were somewhat heterogeneous with some differences in patient populations and intensity of treatment. A wide range of inspiratory pressures (10 - 22 $cmH_20$) was employed and the range of sample size completing the protocols on treatment was only 6 to 14 patients. One small randomized study with sham PAP in a control group addressed adherence and acceptance.[149] Adherence determined by timers was not different between sham and bilevel PAP. However, more than 50% of patients dropped out at 3 months in the bilevel PAP arm without attrition in the sham PAP group. This raises substantial concerns regarding long-term acceptance of bilevel PAP in COPD patients. In another study,[154] patients with mild sleep-disordered breathing were included (average AHI =10). Comparison of the AHI in the patient group in this study with the 3 other studies is problematic because variable or unspecified definitions of hypopnea were used. Changing the threshold for definition of hypopneas can substantially change the numeric value of AHI.[163] Unlike methods developed for adjusting bilevel PAP to improve objective measures of respiratory distress in acute respiratory failure during wakefulness, none of the Level II studies employing bilevel PAP during sleep employed titration of pressures to a targeted level of nocturnal gas exchange or sleep parameters.

The results of these 4 heterogeneous Level II studies were inconsistent and employed different outcome measures. Three of these studies[149,152,153] show no effect of bilevel PAP on daytime gas exchange whereas 1 study[154] demonstrated improvement in both nocturnal and daytime $PaO_2$ and $PaCO_2$ (daytime $PaO_2$ + 5.9 mmHg [effect size .9] and $PaCO_2$ - 4.5mmHg [effect size .8]) as well as an improvement in quality of life scores. Total sleep time and sleep efficiency were improved in 2 studies[152,154] that used relatively high inspiratory pressures (18 and 22 cm $H_20$) and either failed to improve or deteriorated in 2 studies[149,153] employing relatively low inspiratory pressures (10 and 12 cm $H_20$). Since none of the studies with negative findings included a power analysis, there is a reasonable probability of a Type II error. It is unclear whether the inconsistent results of these RCTs of bilevel PAP during sleep reflect differences in patient selection, differences in the methods of treatment that were employed, or the possibility that COPD patients with stable hypercapnic respiratory failure derive less benefit than patients with acute respiratory failure. In addition, the relatively small sample sizes employed and the failure of the protocols to adjust pressures to a targeted effect during sleep significantly increases the likelihood of false negative results in these studies. However, improved sleep quality in positive studies suggest that higher inspiratory pressures may be more effective than lower pressures.

#### 7.3.3 Efficacy of Bilevel PAP in Patients with Restrictive Disease

Eight Level III studies[84,148,150,151,155,156,158,160] have addressed the use of bilevel PAP with a wide variety of restrictive lung disorders. Most of these studies have heterogeneous patient populations with a mixture of neuromuscular diseases and chest wall restriction. With chronic nocturnal bilevel PAP, improvement in daytime hypercapnia was noted in 3 of 4 studies that evaluated daytime gas exchange.[148,151,156] Daytime respiratory muscle strength increased in both studies which evaluated this parameter.[148,156] The only study evaluating objective daytime sleepiness demonstrated an improvement in MSLT after chronic nocturnal bilevel PAP in neuromuscular disease.[150] In an analysis of residual effects of prolonged ventilatory support on sleep and gas exchange, 1 study demonstrated that nocturnal gas exchange and distribution of sleep stages were improved (as compared to baseline) after 6 and 12 months of chronic ventilatory support even on a night when bilevel PAP was withheld.[160] The same author has shown that patients with restrictive disease have improvements in respiratory muscle and exercising muscle endurance following 3 months chronic nocturnal ventilatory support[164] and improvements in mean pulmonary artery pressure after 1 year of chronic nocturnal ventilatory support,[164,165] though these studies were not included in the evidence grading because a mixture of volume cycle and bilevel PAP was employed. One Level III study demonstrated a substantial improvement in 1 year mortality in patients with amyotrophic lateral sclerosis with a vital capacity of 40 ± 21% of predicted who were treated with undisclosed levels of bilevel PAP as compared to patients treated with oxygen and "palliative" measures.[155]

#### 7.3.4 Summary

There is no evidence that bilevel PAP improves efficacy or adherence in the management of OSA in first time users of PAP but the evidence thus far at least supports equivalency for efficacy and adherence. There is limited evidence that patients with coexisting lung disease or hypercapnia prefer and show some gas exchange benefit with bilevel PAP as compared to CPAP.

Bilevel PAP improves gas exchange and sleep in patients with restrictive lung disease based on studies with Level III evidence. Current evidence regarding efficacy of PAP employed during sleep in COPD patients is limited to a small number of conflicting studies with Level II and III evidence employing different outcome measures. The practice of employing arbitrary levels of PAP for treatment of hypercapnic COPD patients, particularly at relatively low levels of inspiratory pressure, may not improve sleep quality or gas exchange.

#### 7.3.5 Future Research

Additional larger RCTs with cross-over design should be performed to substantiate the 2 negative outcome studies comparing efficacy and patient adherence with bilevel PAP vs. CPAP in patients with OSA who do not have coexisting respiratory disease. The use of bilevel PAP in patients with respiratory disease needs to be better defined. Randomized sham-controlled trials of bilevel PAP in patients who have OSAHS in the setting of coexisting respiratory disease should be performed to determine whether the positive outcomes of the existing Level III studies could be substantiated. Patient stratification or selection criteria could be designed to help develop guidelines for specific patient groups such as hypercapnic and non-hypercapnic patients or for specific diagnoses such as COPD, neuromuscular disease, or restrictive rib cage disease.

In chronic respiratory failure complicating COPD, the pressure prescription in randomized controlled trials of bilevel PAP during sleep needs to parallel more closely the designs of bilevel PAP in acute respiratory failure with higher inspiratory pressures or adjustment of pressures to a desired effect. In addition, adher-

ence and immediate and delayed outcomes should be examined. Randomized sham-controlled trials of bilevel PAP in patients who have restrictive lung disease could help to determine whether the existing Level III studies with positive outcomes can be substantiated.

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