Continuous Positive Airway Pressure for Treatment of Obstructive Sleep Apnea in Stroke Survivors
What Do We Really Know?

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Obstructive sleep apnea (OSA) has serious cardiovascular consequences and increases the risk of stroke.1,2 OSA is common in patients with stroke3,4 and is associated with impaired quality of life, reduced cognitive function, and excessive fatigue,5,6 conditions that are common in stroke victims and that may delay poststroke recovery.6,7 It is possible that treating OSA could improve clinical recovery in patients with stroke.

Continuous positive airway pressure (CPAP) is the “gold standard” treatment for OSA; however, there have been few studies of CPAP use in patients poststroke, and the ability for CPAP to definitively improve outcomes has yet to be established in this population. Part of the motivation for this review stems from our experience with a clinical trial that closed due to futility.1 As a “postmortem” on the trial’s closure, we scrutinized the literature, summarizing outcome data in the area and considering recruitment experience in similar trials. Finally, we comment on possible study design characteristics that might make future trials more successful.

CPAP Treatment in Stroke Survivors

Number of Studies
A PubMed search up to November 2011 using the terms stroke OR transient ischemic attack AND apnea AND continuous positive airway pressure revealed 17 published studies (online-only Data Supplement Table I). Studies were heterogeneous with regard to timing of treatment onset, follow-up assessment timing, and outcomes studied, making a meta-analysis inappropriate; therefore, we conducted a systematic qualitative review of the literature.

Nine studies were observational,11–19 3 of which examined the same cohort of patients over time.16–18 Six studies randomized patients to CPAP versus treatment as usual (TAU),20–26 and one study randomized patients to CPAP or sham CPAP.27 On average, studies followed a small number of patients: observational studies included a median of 22 patients who had been prescribed CPAP treatment and randomized controlled trials (RCTs) included a median of 50 patients who were randomized to CPAP or control.

Timing of CPAP Intervention
It is conceivable that findings may be influenced by the timing of the CPAP intervention vis-à-vis the stroke onset. All studies were initiated in acute hospital stroke units or rehabilitation units. There was variability in the time between stroke and study enrollment with patients recruited between 48 hours and 2 months poststroke. Studies also varied widely in length with follow-up periods ranging from 1 night to 7 years.14,16

Outcomes
Online-only Data Supplement Table I includes a detailed review of duration, main outcomes, and findings from each of the studies included in this review.

Recruitment, Acceptability, and Adherence
Eight studies investigated treatment adherence and/or acceptability as a primary outcome with the duration of trials ranging from 1 night to 60 months.11–15,19,20,21 A common theme across studies was that CPAP recruitment was challenging and adherence at follow-up was poor. In short-term observational studies (1 night to 2 months), 50% to 100% of subjects prescribed CPAP were described as adherent throughout the study period.12–15 However, observational studies with longer-term follow-up periods (18 months to 7 years) reported significantly higher attrition with adherence at follow-up ranging from 8% to 29%.11–18

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Recruitment into randomized studies appeared particularly challenging; investigators reported screening hundreds of potential participants but enrolling relatively low percentages. Of participants who were considered for inclusion into an RCT, 70% had at least one exclusionary criteria.20–22,26,27 When approached, 55% of patients without an exclusionary criteria refused to participate.20–22,26,27 Of the participants randomized to CPAP intervention, for which adherence data were available (N=165), 48% of those assigned to CPAP were adherent at the last assessment point (online-only Data Supplement Tables II and III).

Randomized studies ranged from 1 to 3 months in duration and the total percentage of participants who underwent screening and were available for follow-up was typically 4% to 13%.20–24,26 Of the 3473 participants screened in the RCT studies, only 2.3% were CPAP-adherent at the last assessment point (Figure). The Figure illustrates the difficulty associated with isolating a patient population that is eligible, willing to participate in a study, and compliant with the rigors of this type of treatment study.

The literature offers little guidance as to “why” the adherence is so poor. The most commonly cited factors associated with poor adherence were poststroke-related neurological impairments, patient dependency, and lack of an available caregiver to assist with CPAP use.13–15,17,22,24 Mask discomfort, subjective sleep disturbance, and claustrophobia were also listed by several investigators as reasons for nonadherence.14,15,22 In some studies, increased pretreatment sleepiness was associated with better adherence14,17; however, this finding was not consistently found.15 Finally, one study reported that higher depressive symptoms were associated with worse CPAP adherence.22

Cardiovascular Events After Stroke

Three studies investigated whether CPAP use was associated with reductions in subsequent cardiovascular events and mortality. One observational study found that in patients with stroke with OSA, CPAP nonadherence was associated with a significant increase in new vascular events in comparison to those who adhered to CPAP or did not have OSA.16,17 Additionally, patients who were nonadherent to CPAP had an increased risk of mortality at 5-year follow-up compared with the other groups.18 One RCT found no differences in vascular events between patients randomized to CPAP versus TAU after 3 months.20 Contrastingly, another RCT found that CPAP versus TAU was associated with a longer time to the next cardiovascular event (14.9 versus 7.9 months); however, cardiovascular mortality was similar between groups at 2-year follow-up.25

Neurological and Psychological Recovery From Stroke

Four studies investigated whether CPAP treatment was associated with improved neurological recovery from stroke, improvements in activities of daily living, or reductions in sleepiness and depression. In 2 studies, CPAP compared with TAU was not associated with significant gains in cognitive functioning (assessed with the Mini-Mental Status Examination or Addenbrooke’s Cognitive Examination).22,24 One study reported that CPAP treatment compared with TAU over 1 month was associated with improvements in stroke-related impairments (Canadian Neurological Scale) but not in the 6-minute walk test, attention, or executive functioning.26 One study found that CPAP treatment over 1 month compared with TAU was associated with better stroke-related recovery (assessed by the National Institute of Health Stroke Scale).21 Finally, 1 month poststroke, CPAP compared with TAU was associated with greater neurological improvement,
assessed by the Rankin and Canadian scales, but these differences were indiscernible at 24-month follow-up.25 Three studies comparing CPAP with TAU failed to find improvements in activities of daily living assessed with the Barthel Index.22,24,25

CPAP compared with TAU was not associated with significant changes in sleepiness or subjective health status in one study.22 Similarly, no difference in sleepiness or depressive symptoms were observed in patients randomized to CPAP or sham CPAP over 3 months.27 In contrast, one study found that compared with TAU, CPAP treatment over 1 month was associated with an improvement in depressive symptoms.24 Another investigation found that CPAP treatment over 1 month compared with TAU was associated with improvements in sleepiness and the affective component of depression.26

Discussion

This review suggests that the benefits of CPAP treatment in patients with stroke are far from clear. There is some encouraging preliminary evidence that CPAP use for longer periods of time (1.5, 2, and 7 years) may be associated with delayed onset of new cardiovascular incidents poststroke16,17,25; however, none of the studies examining cardiovascular outcomes used an active control group. The question also remains, was higher patient impairment at study onset associated with both nonadherence and negative health consequences in the observational studies?

Disappointingly, no studies found that CPAP was associated with improvements in activities of daily living over 1- to 3-month follow-up periods and it is unsettled whether CPAP use improves neurological recovery poststroke.22,24,27 It may be that it is inappropriate to use brief and/or broad measures of neurological recovery as the marker of treatment efficacy (eg, mental status examinations). For instance, visual field cuts or hemiparesis may never respond to CPAP, whereas one could speculate that executive function may improve. Lack of consistent significant findings regarding cognitive tests may reflect differing levels of sensitivity of the tests across studies; more nuanced neuropsychological testing might reveal aspects of functioning that CPAP effects.

The evidence regarding CPAP’s ability to improve sleepiness and depression after stroke was also mixed. Given the heterogeneity of patients with stroke and the complicated milieu of comorbid medical and psychological problems affecting the population, it may be that specific patient subsets are more likely to show improvements in sleepiness/depression with CPAP use. This same logic likely pertains to cardiovascular and neuropsychological changes.

Enrollment and patient retention was a major challenge. Of the >3000 patients approached to participate in RCTs investigating the effects of CPAP for OSA poststroke, <3% were adherent to CPAP at study conclusion (Figure). Stroke-related impairment, mask discomfort, sleep disturbances, and claustrophobia were common reasons for nonadherence. Additionally, in our trial, we found many patients with stroke refused initial treatment because they were too overwhelmed by the stroke and associated recovery activities.

Given the inconsistent findings, the potential selection bias of patients electing to comply with CPAP (eg, potentially less serious stroke impairments, fewer communication barriers) and the known impact of placebo on outcomes, it is still unclear whether CPAP is associated with improved stroke-related cardiovascular, psychological, and neuropsychological outcomes.

Power

An issue that limited many studies was lack of available power. For example, Bravata et al20 noted a trend in their data, which suggested that the vascular event rate was lower in participants using CPAP compared with controls; they also noted that increasing CPAP adherence was associated with a lower event rate (P=0.08). Similarly, Parra et al25 reported that cardiovascular mortality rates were lower in the CPAP arm than the control group (P=0.16). However, both sets of authors commented that they were underpowered to detect a significant change in the outcome variable. Small sample sizes and associated power limitations cloud the interpretation of many of the null findings reported in the literature. Unfortunately, the need for increased sample sizes is made difficult by issues of recruitment and retention.

Future Directions

This review raises many questions about the state of the research and how to proceed with future trials. A vast number of patients were screened across studies, yielding relatively low enrollment and completion numbers. Such recruitment challenges are typical for RCTs in patients with stroke.28 For instance, in a meta-analysis of acute stroke trials, the recruitment rate across North America was only 0.57 patients per month.29

Strategic Enrollment

Given the low enrollment, sample heterogeneity makes it difficult to observe effects. In small trials, imbalance in key covariates between treatment arms (eg, severity of stroke) could confound treatment effects. A standard approach to ensure balanced randomization arms is to stratify randomization on key covariates. However, this is only feasible if the number of strata is small, which may not be the case in stroke studies in which many patient factors could influence outcomes. A possibly better alternative for sleep treatment trials in patients with stroke would be to use covariate-adaptive randomization,30 in which a participant’s treatment allocation is based on the covariate distributions observed thus far.

Patients with stroke are often hesitant to participate in a sleep study. Given there is so much reluctance, it may be possible that one can screen, preliminarily, for the existence of pre-existing OSA by querying the stroke patient’s spouse or bed partner.

CPAP may not be the appropriate treatment for everyone with OSA after stroke. If a target population that can manage the device could be identified, the field could then begin to study the characteristics that define people who have the highest likelihood of benefitting. Even if the target population is restricted on clinical grounds, there may be so much variability in baseline and in changes in outcome variables that it is difficult to show statistically significant differences versus TAU or sham CPAP. Because it is not clear that
patients with certain stroke subtypes or locations are more or less likely to benefit from OSA intervention, it may not yet be possible to focus on a population that has the best chance of responding to the intervention. Thus, large sample sizes with high treatment adherence at study completion are necessary.

Even in studies with relatively liberal inclusionary criteria, patients with significant neurological deficits such as neglect or language impairment may not be able to adhere to the therapy or be able to consent for such studies. Furthermore, the degree of such patients’ communication impairments would make it difficult to obtain any but the coarsest of characterizations of quality of life and functioning.

**Multicenter Enrollment**
Given the limitations of expected tolerability and patient availability, no single center is likely to recruit a large enough sample. Although a number of design modifications may be able to increase yield, future studies will need access to a large number of stroke survivors. Given our experience and those reported in various published studies, one may assume that only 5% to 10% of patients with stroke may be willing to be in such a study. The rest would be ineligible due to factors such as severity of stroke or seriously confounding other illnesses/conditions (eg, dementia) or would be unwilling to enroll in a study that was interpreted as having questionable benefit.

**Diagnosis**
There is a difference of opinion in the field whether a full polysomnogram is necessary to diagnose OSA or whether a more abbreviated sleep study may be adequate. A full polysomnogram provides precise information on sleep characteristics, which might answer some research questions, but the full polysomnogram imposes greater response burden on patients. We have seen patients who were feeling so overwhelmed by their stroke and so tired from rehabilitation activities that they refused a polysomnogram because of their fear that it would leave them all the more exhausted.

**Treatment Comparison**
Interestingly, the type of comparison treatment selected for the contrast with CPAP may affect enrollment. Although a placebo–CPAP intervention may be the optimal theoretical placebo comparison in terms of treatment expectancy, informing potential patients with stroke that they may be randomized to a placebo–CPAP intervention may just be “too much” for them to consider given the patient burden of CPAP treatment. In comparison, studies that merely randomized patients to receive either CPAP or standard stroke rehabilitation may be more acceptable to patients. Alternatively, OSA treatment devices such as dental retainers may be better tolerated and could potentially serve as an alternative treatment.

**Treatment Choices**
There may be subtle but important problems in fitting CPAP masks to patients with stroke. It is conceivable that patients with stroke will have problems with mouth leaks if nasal or nasal pillow CPAP masks are used due to frequent facial hemiparesis after a stroke. In such cases, the use of a full-face CPAP mask that covers the nose and mouth or a total facemask that covers the entire face (eyes, nose, mouth) may be more efficacious. It also makes sense that simpler systems requiring less complex motor skills would be easier for patients with stroke to use and there is some evidence that a one-piece head frame system versus traditional strap headgear is easier for patients to use.31

It is also unclear if CPAP or bilevel continuous airway pressure would be more effective or tolerable for stroke survivors with hemiplegia who often have weakness of the diaphragm and accessory muscle of respiration, including the abdominal muscles, which results in a restrictive respiratory pattern, hypoventilation, and often hypoxia.32,33 The sensation of not being able to easily exhale is a common complaint of new CPAP users that, if not addressed, often results in CPAP intolerance. Some patients with OSA tolerate a bilevel continuous airway pressure setup better, because it gives the sensation that exhalation is easier. Evaluation of respiratory function poststroke is not routine. However, in the setting of OSA and stroke, evaluation of respiratory muscle strength and respiratory function may be useful to guide the clinician in the choice of CPAP or bilevel continuous airway pressure to treat OSA in this population; however, there is no prior research to guide recommendations.

**Adherence**
Adherence with CPAP is a challenge and appears to be particularly difficult for patients with stroke. First off, the patient needs to be able to perceive a benefit to treatment. Patients with stroke may be just too overwhelmed by their strokes to consider short- or long-term benefits of CPAP. In addition, problems with mask-fitting or the ability to manage the device is a likely barrier for many patients.

Adherence of another kind—staff and caregiver compliance with CPAP—can also be a challenge on a rehabilitation unit. Nursing staff on such units may be relatively unfamiliar and resistant to CPAP apparatus at the bedside. Careful in-service training is necessary to ensure that the prescribed CPAP is actually offered to the patient each night. Staff hesitations in the arenas of time constraints, lack of perceived benefits, and/or concerns about patient burden may translate into poorer compliance on the part of the patient. Of equal importance is the education that must be provided to caregivers once the patient with stroke is discharged from the hospital. Given the widespread impairments associated with many strokes, it may be unrealistic to expect that patients will continue CPAP use on their own after discharge. For this reason, it will be important to educate caregivers about CPAP and to understand what types of support they need to maximize their compliance with CPAP administration.

**Conclusions**
Stroke is a heterogeneous disease extending across various ages, comorbidities, and stroke severity. Perhaps at the far extreme of severity, CPAP may do little to improve functional outcomes and quality of life. However, at this point, we do not know whether stroke survivors with differing levels
of impairment (mild, severe) may benefit differentially from treatment. In the future, studies of recovery will need to be powered to recognize this heterogeneity as well as the heterogeneity of the patient’s other health conditions that may affect cognitive and quality-of-life indicators. It is possible for instance that certain types of strokes may be associated with greater or lesser benefits from CPAP. As a practical matter, severe cognitive or sensorimotor impairments may preclude managing CPAP on one’s own, so ability to even attempt the treatment may improve after initial stroke recovery. Similarly, it is not established how long treatment should continue, although CPAP is typically prescribed for chronic treatment.

OSA is common in patients with stroke, and CPAP use entails substantial subject burden; however, the question remains unanswered whether patients with stroke will in fact even use CPAP once they are out of the hospital. This leads to a Catch-22: until it is clearer that CPAP can be shown to enhance outcomes after stroke, it is unlikely that patients will be motivated to try this intervention, yet it is difficult to show benefit if researchers or clinicians cannot get sufficient numbers of patients with stroke to wear CPAP long enough to show improvements. If anything, findings from this review demonstrate the importance of controlled comparisons. Because so many questions remain unanswered, multisite studies with large numbers of patients may be the only way to find out if CPAP helps these patients.

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**Disclosures**

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**References**


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<table>
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<tr>
<th>Author</th>
<th>Duration</th>
<th>Received CPAP (N)</th>
<th>Outcome Variables</th>
<th>Significance</th>
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<tr>
<td>Bassetti et al., (2006)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>60+/−16 months</td>
<td>70</td>
<td>Treatment adherence</td>
<td>Eight patients (11%) were CPAP adherent at follow-up. Of those patient discharged from the hospital using CPAP, (31%) were adherent at follow CPAP was “accepted” by 13 (81%) patients and “well tolerated” in eight (50%)</td>
</tr>
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<td>Broadley et al. (2007)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NA</td>
<td>16</td>
<td>Treatment adherence</td>
<td>CPAP resulted in “normalization of oxygen saturation” in all patients Treatment was “tolerated well”.</td>
</tr>
<tr>
<td>Disler et al., (2002)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NA</td>
<td>5</td>
<td>Oxygen saturation</td>
<td>CPAP adherence associated with fewer new vascular events (6.7% vs 36.1%; <em>p</em> = 0.03).</td>
</tr>
<tr>
<td>Martinez-Garcia, et al., (2005)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>18 months</td>
<td>15 vs 36 (CPAP non-adherent)</td>
<td>New vascular events</td>
<td>CPAP adherence was associated with decreased risk of mortality (49.6 % 68.3%; HR = 1.58; <em>p</em> = 0.04).</td>
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<tr>
<td>Martinez-Garcia et al (2009)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>5 years</td>
<td>28 vs 68 (CPAP non-adherent)</td>
<td>Mortality</td>
<td>CPAP adherence was associated with decreased risk of non-fatal CVE (17.9% vs 38.2%; HR = 2.87; <em>p</em> = 0.03).</td>
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<tr>
<td>Martinez-Garcia et al. (epub)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>7 years</td>
<td>28 vs 68 (CPAP non-adherent)</td>
<td>Non-fatal CVE</td>
<td>CPAP adherence was associated with decreased risk of non-fatal CVE (17.9% vs 38.2%; HR = 2.87; <em>p</em> = 0.03).</td>
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<tr>
<td>Palombini &amp; Guilleminault (2006)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>8 weeks</td>
<td>32</td>
<td>Treatment adherence</td>
<td>Seven patients (22%) were CPAP adherent at follow-up.</td>
</tr>
<tr>
<td>Scala et al. (2009)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>1 night</td>
<td>12</td>
<td>Treatment adherence</td>
<td>Ten patients (84%) agreed to try CPAP; of those five (42%) used CPAP ≥6 hours, five (42%) used CPAP for 1-3 hours.</td>
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<tr>
<td>Wessendorf et al. (2001)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>10 days</td>
<td>105</td>
<td>24-h Blood Pressure (BP)</td>
<td>16 patients underwent 24-h BP monitoring. CPAP was associated with decreased nocturnal BP in CPAP compliant patients (N=11) compared to noncompliant patients (N=5) (∆-8 vs ∆0.8, <em>p</em> =0.04). There was no difference in mean daytime BP between groups (∆-4.3 vs ∆-6.8, <em>p</em> =0.57).</td>
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<td></td>
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<td></td>
<td>Subjective wellbeing</td>
<td>Subjective wellbeing was assessed in 41 patients. CPAP use was associated with improvements compared to controls (∆26 vs ∆2, <em>p</em> =0.02)</td>
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<td></td>
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<td>Treatment acceptance</td>
<td>74/105 patients (70.5%) agreed to CPAP titration</td>
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### Randomized Studies (CPAP group/Control Group (Treatment as Usual))

<table>
<thead>
<tr>
<th>Study</th>
<th>Time</th>
<th>Patients</th>
<th>Adherence to auto-CPAP</th>
<th>Recurrent vascular event rate</th>
<th>National Institutes of Health Stroke Scale (NIHSS)</th>
<th>Extended Activities of Daily Living (EADL) Total</th>
<th>BI</th>
<th>SF-36 Physical Summary</th>
<th>SF-36 Mental Summary</th>
<th>SF-36</th>
<th>Canadian Scale</th>
<th>Rankin Scale</th>
<th>SF-36</th>
<th>Treatment acceptance/adherence BI</th>
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</thead>
<tbody>
<tr>
<td>Bravata et al. (2010)</td>
<td>3 months</td>
<td>30/12</td>
<td>Adherence to auto-CPAP</td>
<td>Recurrent vascular event rate</td>
<td>National Institutes of Health Stroke Scale (NIHSS)</td>
<td>Extended Activities of Daily Living (EADL) Total</td>
<td>BI</td>
<td>SF-36 Physical Summary</td>
<td>SF-36 Mental Summary</td>
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<td>SF-36</td>
<td>Treatment acceptance/adherence BI</td>
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<tr>
<td>Bravata et al. (2011)</td>
<td>1 month</td>
<td>31/24</td>
<td>National Institutes of Health Stroke Scale (NIHSS)</td>
<td>CPAP use associated with greater improvements on the NIHSS (Δ-3.0) than control (Δ-1.0) (p = 0.03).</td>
<td>CPAP use, compared to control, was not associated with improvements in the EADL total at 6-month follow-up (28 vs 23, p = 0.50)</td>
<td>CPAP use, compared to control, was not associated with improvements in the SF-36 Physical Summary at 6-month follow-up (28.4 vs 19.8, p = 0.25)</td>
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<td>Hsu et al. (2006)</td>
<td>8 weeks</td>
<td>15/15</td>
<td>Barthel Index (BI)</td>
<td>CPAP use, compared to control, was not associated with improvements in the BI at 6-month follow-up (18 vs 19, p = 0.64)</td>
<td>CPAP use, compared to control, was not associated with improvements in the SF-36 Physical Summary at 6-month follow-up (28.4 vs 19.8, p = 0.25)</td>
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<td>34/25</td>
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<tr>
<td>Parra et al. (2011)</td>
<td>24 months</td>
<td>71/69</td>
<td>SF-36</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the Canadian scale compared to control (Δ1 vs Δ1.6, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the Canadian scale compared to control (Δ1 vs Δ1.6, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the Canadian scale compared to control (Δ1 vs Δ1.6, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the Canadian scale compared to control (Δ1 vs Δ1.6, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
<td>CPAP use not associated with changes in the SF-36 compared to control (Δ7.5 vs Δ7.8, p &gt; 0.05)</td>
</tr>
</tbody>
</table>

Regular CPAP use (≥70% nights for ≥ 4 hours/night) was observed in 12 patients (40%), 18 patients (60%) had “some use (< 70% nights for < 4 hours/night” and 16 patients (47%) agreed to a CPAP titration study, of which 4 (12%) agreed to continue using CPAP at home.
<table>
<thead>
<tr>
<th>Measure</th>
<th>CPAP Use</th>
<th>Control Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>CPAP associated with longer mean time until next cardiovascular event (versus 7.9 months, ( p = 0.04 ))</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>CPAP use not associated with differences in cardiovascular mortality compared to control (87.7% versus 88.4%, ( p = 0.91 ))</td>
<td></td>
</tr>
<tr>
<td>6-minute walk test</td>
<td>CPAP use was not associated with improvements on the 6-minute walk test compared to controls (Δ113 vs Δ46, ( p = 0.75 ))</td>
<td></td>
</tr>
<tr>
<td>Canadian Scale</td>
<td>CPAP use was associated with improvements on the Canadian scale compared to controls (Δ2.3 vs Δ0.7, ( p &lt; 0.001 ))</td>
<td></td>
</tr>
<tr>
<td>Chedoke-McMaster Stroke Assessment Scale (CMSAS)</td>
<td>CPAP use was marginally associated with improvements on the CMSAS ( \Delta ) subscale (Δ1.1 vs Δ0.5, ( p = 0.08 )) and was associated with improvements on the leg subscale compared to controls (Δ0.8 vs Δ0.4, ( p = 0.001 )). CPAP use was not associated with improvements on the hand (Δ0.7 vs Δ0.7, ( p = 0.92 )) on foot subscales (Δ0.5 vs Δ0.7, ( p = 0.64 ))</td>
<td></td>
</tr>
<tr>
<td>Functional Independence Measure (FIM)</td>
<td>CPAP use was marginally associated with improvements on the FIM compared to controls (Δ27.3 vs Δ20.0 ( p = 0.07 ))</td>
<td></td>
</tr>
<tr>
<td>Sustained Attention Response Time (SART)</td>
<td>CPAP use was not associated with improvements on the SART, total ( n ) of false positive errors (Δ2 vs Δ-1, ( p = 0.26 )) or mean RT in the 4 trials before false press (Δ12 vs Δ-51, ( p = 0.26 )) compared to controls</td>
<td></td>
</tr>
<tr>
<td>Digit + visual spatial span-forward</td>
<td>CPAP use was not associated with improvements on the Digit = visual spatial span-forward (Δ3 vs Δ-3, ( p = 0.27 )) or span-backward (Δ10 vs Δ5, ( p = 0.32 )) compared to controls</td>
<td></td>
</tr>
<tr>
<td>Purdue Pegboard</td>
<td>CPAP use was not associated with improvements on the Purdue Pegboard dominant hand score (Δ3 vs Δ6, ( p = 0.88 )), nondominant hand score (Δ4 vs Δ4, ( p = 0.37 )) or affected hand score (Δ4 vs Δ7, ( p = 0.62 )) compared to controls</td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>CPAP use was not associated with improvements on the somatic component of the BDI (values not reported). A significant reduction in the affective component was observed, compared to controls (Δ-2.6 vs Δ-1.4, ( p = 0.001 ))</td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (ESS)</td>
<td>CPAP group showed improvements on the ESS compared to controls (Δ0 vs Δ-1, ( p &lt; 0.0001 ))</td>
<td></td>
</tr>
<tr>
<td>Stanford Sleepiness Scale (SSS)</td>
<td>CPAP group showed improvements on the SSS compared to controls (Δ1 vs Δ0, ( p = 0.05 ))</td>
<td></td>
</tr>
<tr>
<td>BI</td>
<td>CPAP use not associated with changes in the BI compared to control (Δ1 vs Δ1.1, ( p = 0.98 ))</td>
<td></td>
</tr>
<tr>
<td>Delirium (%)</td>
<td>CPAP use not associated with changes in delirium compared to control (, Ryan et al. (2011)¹⁵, 1 month, 22/22</td>
<td></td>
</tr>
<tr>
<td>Delirium (%)</td>
<td>CPAP use not associated with changes in delirium compared to control (, Sandberg et al., (2001)¹⁶, 1 month, 33/30</td>
<td></td>
</tr>
</tbody>
</table>
### Mini-Mental Status Exam (MMSE)

CPAP use not associated with improvements on the MMSE compared to control (Δ2.6 vs Δ2.8, \( p = 0.77 \))

### Montgomery-Asberg Depression Rating Scale (MADRS)

CPAP use associated with greater improvements on the MADRS than control (Δ-5.4 vs Δ1.8, \( p < 0.01 \)).

---

**Randomized Study (CPAP group/Control Group Sham CPAP)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (epub)(^{17})</td>
<td>3 months</td>
<td>15/17</td>
<td>CPAP use not associated with changes on the BI compared to control (95 vs 100, ( p &gt; 0.05 ))&lt;br&gt;CPAP use not associated with improvements on the ESS compared to control (8 vs 7, ( p &gt; 0.05 ))&lt;br&gt;CPAP use not associated with changes on the FSS compared to control (12.6 vs 2.4, ( p &gt; 0.05 ))&lt;br&gt;CPAP use not associated with changes on the PHQ-9 compared to control (5 vs 2, ( p &gt; 0.05 ))&lt;br&gt;CPAP use not associated with changes on the NIHSS compared to control (1 vs 2, ( p &gt; 0.05 ))&lt;br&gt;CPAP use not associated with changes on the SF-36 compared to control (173 vs 171, ( p &gt; 0.05 )).</td>
</tr>
</tbody>
</table>

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Addenbrooke’s Cognitive Examination; ADL = activities of daily living; BDI = Beck Depression Inventory; BI = Barthel Index; BP = blood pressure; CMSAS = Chedoke-McMaster Stroke Assessment Scale; CPAP = continuous positive airway pressure; CVE = cardiovascular events; EADL = Extended Activities of Daily Living; ESS = Epworth Sleepiness Scale; FIM = Functional Independence Measure; FSS = Fatigue Severity Score; MADRS = Montgomery-Asberg Depression Rating Scale; MMSE = Mini-Mental Status Exam; NA = Not available; NIHSS = National Institutes of Health Stroke Scale; FSS = Fatigue Severity Score; PHQ-9 = Patient Health Questionnaire; SSS = Stanford Sleepiness Scale; SART = Sustained Attention Response Time; SF-36 = Short Form-36 quality of life questionnaire; TAU = Treatment as usual.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Duration</th>
<th>Potential Participants N</th>
<th>Assigned to Sleep Study N</th>
<th>Diagnosed with OSA N *</th>
<th>Prescribed CPAP N</th>
<th>CPAP Adherent in Hospital N</th>
<th>CPAP Adherent at Last Follow-up Point N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassetti et al., (2006)¹</td>
<td>60 +/- 16 months</td>
<td>NA</td>
<td>152</td>
<td>70</td>
<td>70</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>Broadley et al., (2007)²</td>
<td>6 weeks</td>
<td>81</td>
<td>57</td>
<td>23</td>
<td>16</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>Disler et al., (2002)³</td>
<td>NA</td>
<td>38</td>
<td>38</td>
<td>19</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Martinez-Garcia, et al., (2005)⁴</td>
<td>18 months</td>
<td>139</td>
<td>95</td>
<td>51</td>
<td>51</td>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td>Martinez-Garcia et al (2009)⁵</td>
<td>5 years</td>
<td>223</td>
<td>166</td>
<td>96</td>
<td>96</td>
<td>NA</td>
<td>28</td>
</tr>
<tr>
<td>Martinez-Garcia et al. (epub)⁶</td>
<td>7 years</td>
<td>2 months</td>
<td>50</td>
<td>21</td>
<td>14</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Palombini &amp; Guilleminault (2006)⁷</td>
<td>1 night</td>
<td>NA</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Scala et al. (2009)⁸</td>
<td>10 days</td>
<td>NA</td>
<td>105</td>
<td>105</td>
<td>74</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* OSA criteria varied by study team from AHI ≥ 5/hour to AHI ≥ 30/hour. Our table reflects the individual study diagnosis criteria.
NA = Not available
Table 3. Recruitment and Retention in Randomized Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Duration</th>
<th>Potential Participants N</th>
<th>Potential Participants w/o exclusionary criteria N</th>
<th>Refused to Participate</th>
<th>Assigned to Sleep Study</th>
<th>Diagnosed with OSA N *</th>
<th>Randomized to CPAP/Control</th>
<th>Available for Follow-up Assessment N</th>
<th>CPAP Adherent at Last Follow-up Point N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Studies, Control Group TAU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bravata et al. (2010)</td>
<td>3 months</td>
<td>360</td>
<td>213</td>
<td>137</td>
<td>70</td>
<td>42</td>
<td>30/12</td>
<td>NA</td>
<td>12 **</td>
</tr>
<tr>
<td>Bravata et al. (2011)</td>
<td>1 month</td>
<td>955</td>
<td>199</td>
<td>144</td>
<td>55</td>
<td>28</td>
<td>15/13</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Hsu et al. (2006)</td>
<td>2 months</td>
<td>658</td>
<td>96</td>
<td>25</td>
<td>71</td>
<td>33</td>
<td>15/15</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Hui et al., (2002)</td>
<td>NA</td>
<td>80</td>
<td>NA</td>
<td>NA</td>
<td>51</td>
<td>34</td>
<td>34/25</td>
<td>NA</td>
<td>4</td>
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<tr>
<td>Parra et al. (2011)</td>
<td>24 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>235</td>
<td>140</td>
<td>71/69</td>
<td>126</td>
<td>NA</td>
</tr>
<tr>
<td>Ryan et al. (2011)</td>
<td>1 month</td>
<td>466</td>
<td>194</td>
<td>91</td>
<td>103</td>
<td>48</td>
<td>25/23</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Sandberg et al., (2001)</td>
<td>1 month</td>
<td>151</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>63</td>
<td>31/28</td>
<td>59</td>
<td>16 **</td>
</tr>
<tr>
<td><strong>Randomized Study, Control Group Sham CPAP</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al. (epub)</td>
<td>3 months</td>
<td>803</td>
<td>264</td>
<td>133</td>
<td>87</td>
<td>54</td>
<td>15/17</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

* OSA criteria varied by study team from AHI >/= 5/hour to AHI >/= to 30/hour. Our table reflects the individual study diagnosis criteria.

** Defined as CPAP use for longer than 4 hours/night

NA = Not available
References


