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# A sleeping beast: Obstructive sleep apnea and stroke

## ABSTRACT

Up to two-thirds of patients who have had a stroke have obstructive sleep apnea (OSA) afterward. These patients have worse outcomes than those without OSA in terms of short-term morbidity, functional and cognitive recovery, and mortality rates over the long term. Following a stroke, identifying OSA and treating it with positive airway pressure, if possible, are important clinical goals.

## KEY POINTS

A low threshold for evaluating for OSA after a stroke is warranted: the prevalence is high in this population, and risk factors for OSA and its typical clinical picture may not be present.

Questionnaires can help screen for the likelihood of OSA and the need for more definitive assessment with polysomnography or home sleep apnea testing, tests that pose additional challenges after stroke.

Positive airway pressure (PAP) therapy remains the first-line treatment for OSA after stroke; it may improve recovery and reduce long-term sequelae of untreated OSA.

Acceptance of and adherence to PAP therapy can be especially problematic in this population, and alternatives should be considered if needed.

**O**BSTRUCTIVE SLEEP APNEA (OSA) is an independent risk factor for ischemic stroke and may also, infrequently, be a consequence of stroke. It is significantly underdiagnosed in the general population and is highly prevalent in patients who have had a stroke. Many patients likely had their stroke because of this chronic untreated condition.

This review focuses on OSA and its prevalence, consequences, and treatment in patients after a stroke.

## DEFINING AND QUANTIFYING OSA

OSA is the most common type of sleep-disordered breathing.<sup>1,2</sup> It involves repeated narrowing or complete collapse of the upper airway despite ongoing respiratory effort.<sup>3,4</sup> Apneic episodes are terminated by arousals from hypoxemia or efforts to breathe.<sup>5</sup> In contrast, central sleep apnea is characterized by a patent airway but lack of airflow due to absent respiratory effort.<sup>5</sup>

In OSA, the number of episodes of apnea (absent airflow) and hypopnea (reduced airflow) are added together and divided by hours of sleep to calculate the apnea-hypopnea index (AHI). OSA is diagnosed by either of the following<sup>3,4</sup>:

- AHI of 5 or higher, with clinical symptoms related to OSA (described below)
  - AHI of 15 or higher, regardless of symptoms.
- The AHI also defines OSA severity, as follows<sup>3</sup>:
- Mild: AHI 5 to 15
  - Moderate: AHI 15 to 30
  - Severe: AHI greater than 30.

Diagnostic criteria (eg, definition of hypopnea, testing methods, and AHI thresholds) have varied over time, an important consideration when reviewing the literature.

### ■ OSA IS MORE COMMON THAN EXPECTED AFTER STROKE

In the most methodologically sound and generalizable study of this topic to date, the Wisconsin Sleep Cohort Study<sup>6</sup> reported in 2013 that about 14% of men and 5% of women ages 30 to 70 have an AHI greater than 5 (using 4% desaturation to score hypopneic episodes) with daytime sleepiness. Other studies suggest that 80% to 90% of people with OSA are undiagnosed and untreated.<sup>1,7</sup>

The prevalence of OSA in patients who have had a stroke is much higher, ranging from 30% to 96% depending on the study methods and population.<sup>1,8-12</sup> A 2010 meta-analysis<sup>11</sup> of 29 studies reported that 72% of patients who had a stroke had an AHI greater than 5, and 29% had severe OSA. In this analysis, 7% of those with sleep-disordered breathing had central sleep apnea; still, these data indicate that the prevalence of OSA in these patients is about 5 times higher than in the general population.

### ■ RISK FACTORS MAY DIFFER IN STROKE POPULATION

Several risk factors for OSA have been identified.

**Obesity** is one of the strongest risk factors, with increasing body mass index (BMI) associated with increased OSA prevalence.<sup>4,6,13</sup> However, obesity appears to be a less significant risk factor in patients who have had a stroke than in the general population. In the 2010 meta-analysis<sup>11</sup> of OSA after stroke, the average BMI was only 26.4 kg/m<sup>2</sup> (with obesity defined as a BMI > 30.0 kg/m<sup>2</sup>), and increasing BMI was not associated with increasing AHI.

**Male sex and advanced age** are also OSA risk factors.<sup>4,5</sup> They remain significant in patients after a stroke; about 65% of poststroke patients who have OSA are men, and the older the patient, the more likely the AHI is greater than 10.<sup>11</sup>

**Ethnicity and genetics** may also play important roles in OSA risk, with roughly 25% of OSA prevalence estimated to have a genetic basis.<sup>14,15</sup> Some risk factors for OSA such as craniofacial shape, upper airway anatomy, upper airway muscle dysfunction, increased respiratory chemosensitivity, and poor arousal threshold during sleep are likely determined

by genetics and ethnicity.<sup>14,15</sup> Compared with people of European origin, Asians have a similar prevalence of OSA, but at a much lower average BMI, suggesting that other factors are significant.<sup>14</sup> Possible genetically determined anatomic risk factors have not been specifically studied in the poststroke population, but it can be assumed they remain relevant.

Several studies have tried to find an association between OSA and type, location, etiology, or pattern of stroke.<sup>10,11,16-19</sup> Although some suggest links between cardioembolic stroke and OSA,<sup>16,20</sup> or thrombolysis and OSA,<sup>10</sup> most have found no association between OSA and stroke features.<sup>11,12,21,22</sup>

### ■ HOW DOES OSA INCREASE STROKE RISK?

Untreated severe OSA is associated with increased cardiovascular mortality,<sup>21,22</sup> and OSA is an independent risk factor for incident stroke.<sup>23</sup> A number of mechanisms may explain these relationships.

Intermittent hypoxemia and recurrent sympathetic arousals resulting from OSA are thought to lead to many of the comorbid conditions with which it is associated: hypertension, coronary artery disease, heart failure, arrhythmias, pulmonary hypertension, and stroke. Repetitive decreases in ventilation lead to oxygen desaturations that result in cycles of increased sympathetic outflow and eventual sustained nocturnal hypertension and daytime chronic hypertension.<sup>1,5,9,13</sup> Also implicated are various changes in vasodilator and vasoconstrictor substances due to endothelial dysfunction and inflammation, which are thought to play a role in the atherogenic and prothrombotic states induced by OSA.<sup>1,5,13</sup>

Cerebral circulation is altered primarily by the changes in partial pressure of carbon dioxide (Pco<sub>2</sub>). During apnea, the Pco<sub>2</sub> rises, causing vasodilation and increased blood flow. After the apnea resolves, there is hyperpnea with resultant decreased Pco<sub>2</sub>, and vasoconstriction. In a patient who already has vascular disease, the enhanced vasoconstriction could lead to ischemia.<sup>1,5</sup>

Changes in intrathoracic pressure result in distortion of cardiac architecture. When the patient tries to breathe against an occluded

**OSA is an independent risk factor for stroke**

airway, the intrathoracic pressure becomes more and more negative, increasing preload and afterload. When this happens repeatedly every night for years, it leads to remodeling of the heart such as left and right ventricular hypertrophy, with reduced stroke volume, myocardial ischemia, and increased risk of arrhythmia.<sup>1,5,13</sup>

Untreated OSA is believed to predispose patients to develop atrial fibrillation through sympathetic overactivity, vascular inflammation, heart rate variability, and cardiac remodeling.<sup>24</sup> As atrial fibrillation is a major risk factor for stroke, particularly cardioembolic stroke, it may be another pathway of increased stroke risk in OSA.<sup>16,20,25</sup>

### ■ CLINICAL MANIFESTATIONS OF OSA NOT OBVIOUS AFTER STROKE

OSA typically causes both daytime symptoms (excessive sleepiness, poor concentration, morning headache, depressive symptoms) and nighttime signs and symptoms (snoring, choking, gasping, night sweats, insomnia, nocturia, witnessed episodes of apnea).<sup>3,4,26</sup> Unfortunately, because these are nonspecific, OSA is often underdiagnosed.<sup>4,26</sup>

Identifying OSA after a stroke may be a particular challenge, as patients often do not report classic symptoms, and the typical picture of OSA may have less predictive validity in these patients.<sup>1,27,28</sup> Within the first 24 hours after a stroke, hypersomnia, snoring history, and age are not predictive of OSA.<sup>1</sup> Patients found to have OSA after a stroke frequently do not have the traditional symptoms (sleepiness, snoring) seen in usual OSA patients. And they have higher rates of OSA at a younger age than the usual OSA patients, so age is not a predictive risk factor. In addition, daytime sleepiness and obesity are often absent or less prominent.<sup>1,9,27,28</sup> Finally, typical OSA signs and symptoms may be attributed to the stroke itself or to comorbidities affecting the patient, lowering suspicion for OSA.

### ■ OSA MAY HINDER STROKE RECOVERY, WORSEN OUTCOMES

OSA, particularly when moderate to severe, is linked to pathophysiologic changes that can hinder recovery from a stroke.

Intermittent hypoxemia during sleep can worsen vascular damage of at-risk tissue: nocturnal hypoxemia correlates with white matter hyperintensities on magnetic resonance imaging, a marker of ischemic demyelination.<sup>29</sup> Oxidative stress and release of inflammatory mediators associated with intermittent hypoxemia may impair vascular blood flow to brain tissue attempting to repair itself.<sup>30</sup> In addition, sympathetic overactivity and Pco<sub>2</sub> fluctuations associated with OSA may impede cerebral circulation.

Taken together, such ongoing nocturnal insults can lead to clinical consequences during this vulnerable period.

A 1996 study<sup>31</sup> of patients recovering from a stroke found that an oxygen desaturation index (number of times that the blood oxygen level drops below a certain threshold, as measured by overnight oximetry) of more than 10 per hour was associated with worse functional recovery at discharge and at 3 and 12 months after discharge. This study also noted an association between time spent with oxygen saturations below 90% and the rate of death at 1 year.

A 2003 study<sup>32</sup> reported that patients with an AHI greater than 10 by polysomnography spent an average of 13 days longer on the rehabilitation service and had worse functional and cognitive status on discharge, even after controlling for multiple confounders. Several subsequent studies have confirmed these and similar findings.<sup>8,33,34</sup>

OSA has also been linked to depression,<sup>35</sup> which is common after stroke and may worsen outcomes.<sup>36</sup> The interaction between OSA, depression, and poststroke outcomes warrants further study.

In the general population, OSA has been independently associated with increased risk of stroke or death from any cause.<sup>21,22,37</sup> These associations have also been reported in the poststroke population: a 2014 meta-analysis found that OSA increased the risk of a repeat stroke (relative risk [RR] 1.8, 95% confidence interval [CI] 1.2–2.6) and all-cause mortality (RR 1.69, 95% CI 1.4–2.1).<sup>38</sup>

### ■ TESTING FOR OSA AFTER STROKE

Because of the high prevalence of OSA in patients who have had a stroke and the potential

**Obesity is less of a risk factor for OSA in patients after stroke**

for worse outcomes associated with untreated OSA, there should be a low threshold for evaluating for OSA soon after stroke. Objective testing is required to qualify for therapy, and the gold standard for diagnosis of OSA is formal polysomnography conducted in a sleep laboratory.<sup>2-4</sup> Unfortunately, polysomnography may be unacceptable to some patients, is costly, and is resource-intensive, particularly in an inpatient or rehabilitation setting.<sup>28</sup> Ideally, to optimize testing efficiency, patients should be screened for the likelihood of OSA before polysomnography is ordered.

### **Questionnaires can help determine the need for further testing**

Questionnaires developed to assess OSA risk<sup>39</sup> include the following:

**The Berlin questionnaire**, developed in 1999, has 10 questions assessing daytime and nighttime signs and symptoms and presence of hypertension.

**The STOP questionnaire**, developed in 2008, assesses snoring, tiredness, observed apneic episodes, and elevated blood pressure.

**The STOP-BANG questionnaire**, published in 2010, includes the STOP questions plus BMI over 35 kg/m<sup>2</sup>, age over 50, neck circumference over 41 cm, and male gender.

A 2017 meta-analysis<sup>39</sup> of 108 studies with nearly 50,000 people found that the STOP-BANG questionnaire performed best with regard to sensitivity and diagnostic odds ratio, but with poor specificity.

These screening tools and modified versions of them have also been evaluated in patients who have had a stroke.

In 2015, Boulos et al<sup>28</sup> found that the STOP-BAG (a version of STOP-BANG that excludes neck circumference) and the 4-variable (4V) questionnaire (sex, BMI, blood pressure, snoring) had moderate predictive value for OSA within 6 months after stroke.

In 2016, Katzan et al<sup>40</sup> found that the STOP-BAG2 (STOP-BAG criteria plus continuous variables for BMI and age) had a high sensitivity for polysomnographically diagnosed OSA within the first year after a stroke. The specificity was significantly better than the STOP-BANG or the STOP-BAG questionnaire, although it remained suboptimal at 60.5%.

In 2017, Sico et al<sup>41</sup> developed and assessed the SLEEP Inventory (sex, left heart failure, Epworth Sleepiness Scale, enlarged neck, weight in pounds, insulin resistance or diabetes, and National Institutes of Health Stroke Scale) and found that it outperformed the Berlin and STOP-BANG questionnaires in the poststroke setting. The SLEEP Inventory had the best specificity and negative predictive value, and a slightly better ability to correctly classify patients as having OSA or not, classifying 80% of patients correctly.

These newer screening tools (eg, STOP-BAG, STOP-BAG2, SLEEP) can be used to identify with reasonable accuracy which patients need definitive testing after stroke.

### **Pulse oximetry is another possible screening tool**

Overnight pulse oximetry may also help screen for sleep apnea and stratify risk after a stroke. A 2012 study<sup>42</sup> of overnight oximetry to screen patients before surgery found that the oxygen desaturation index was significantly associated with the AHI measured by polysomnography. However, oximetry testing cannot distinguish between OSA and central sleep apnea, so it is insufficient to diagnose OSA or qualify patients for therapy. Further study is needed to examine the ability of overnight pulse oximetry to screen or to stratify risk for OSA after stroke.

### **Polysomnography vs home testing**

Polysomnography is the gold standard for diagnosing OSA. Benefits include technical support and trouble-shooting, determining relationships between OSA, body position, and sleep stage, and the ability to intervene with treatment.<sup>2</sup> However, polysomnography can be cumbersome, costly, and resource-intensive.

A home sleep apnea test, ie, an unattended, limited-channel sleep study, may be an acceptable alternative.<sup>2-4,43,44</sup> Home testing does not require a sleep technologist to be present during testing, uses fewer sensors, and is less expensive than overnight polysomnography, but its utility can be limited: it fails to accurately discriminate between episodes of OSA and central sleep apnea, there is potential for false-negative results, and it can underestimate sleep apnea burden because it does not measure sleep.<sup>2</sup>

**OSA is linked to pathophysiologic changes that could hinder stroke recovery**

Institutional resources and logistics may influence the choice of diagnostic modality. No data exist on outcomes from different diagnostic testing methods in poststroke patients. Further research is needed.

### ■ POSITIVE AIRWAY PRESSURE THERAPY: BENEFITS, CHALLENGES, ALTERNATIVES

The first-line treatment for OSA is positive airway pressure (PAP).<sup>3</sup> For most patients, this is continuous PAP (CPAP) or autoadjusting PAP (APAP). In some instances, particularly for those who cannot tolerate CPAP or who have comorbid hypoventilation, bilevel PAP (BPAP) may be indicated. More advanced PAP therapies are unlikely to be used after stroke.

PAP therapy is associated with reduced daytime sleepiness, improved mood, normalization of sleep architecture, improved systemic and pulmonary artery blood pressure, reduced rates of atrial fibrillation after ablation, and improved insulin sensitivity.<sup>45–49</sup> Whether it reduces the risk of cardiovascular events, including stroke, remains controversial; most data suggest that it does not.<sup>50,51</sup> However, when adherence to PAP therapy is considered rather than intention to treat, treatment has been found to lead to improved cardiovascular outcomes.<sup>52</sup>

#### Mixed evidence of benefits after stroke

Observational studies provide evidence that CPAP may help patients with OSA after stroke, although results are mixed.<sup>53–58</sup> The studies ranged in size from 14 to 105 patients, enrolled patients with mostly moderate to severe OSA, and followed patients from 10 days to 7 years. Adherence to therapy was generally good in the short term (50%–70%), but only 15% to 30% of patients remained adherent at 5 to 7 years. Variable outcomes were reported, with some studies finding improved symptoms in the near term and mixed evidence of cardiovascular benefit in the longer ones. However, as these studies lacked randomization, drawing definitive conclusions on CPAP efficacy is difficult.

Several short-term randomized controlled trials of CPAP have been performed in patients after stroke. A 2018 meta-analysis<sup>59</sup> included 10 such trials with a total of 564

patients (range 30–140 patients), with most having 1 to 3 months of follow-up (range 1 week to over 5 years). Eight of the 10 studies are summarized in **Table 1** (1 study was omitted because many of the patients had central sleep apnea, and 1 was primarily a feasibility study).<sup>60–67</sup>

Patients were enrolled in the index admission or when starting a rehabilitation service—generally 2 to 3 weeks after their stroke. No clear association was found between the timing of initiating PAP therapy and outcomes. All patients had ischemic strokes, but few details were provided regarding stroke location, size, and severity. Exclusion criteria included severe underlying cardiopulmonary disease, confusion, severe stroke with marked impairment, and inability to cooperate. Almost all patients had moderate to severe OSA, and patients with central sleep apnea were excluded.

The major outcomes examined were dropout rates, PAP adherence, and neurologic improvement based on neurologic functional scales (National Institutes of Health Stroke Scale and Canadian Neurologic Scale). As expected, dropout rates were higher in patients randomized to CPAP (OR 1.83, 95% CI 1.05–3.21,  $P = .03$ ), although overall adherence was better than anticipated, with mean CPAP use across trials of 4.5 hours per night (95% CI 3.97–5.08) and with about 50% to 60% of patients adhering to therapy for at least 4 hours nightly.

Improvement in neurologic outcomes favored CPAP (standard mean difference 0.54, 95% CI 0.026–1.05), although considerable heterogeneity was seen. Improved sleepiness outcomes were inconsistent. Major cardiovascular outcomes were reported in only 2 studies (using the same data set) and showed delayed time to the next cardiovascular event for those treated with CPAP but no difference in cardiovascular event-free survival.

#### PAP poses more challenges after stroke

The primary limitation to PAP therapy is poor acceptance and adherence to therapy.<sup>59</sup> High rates of refusal of therapy and difficulty complying with treatment have been noted in the poststroke population, although recent studies have reported better adherence rates. How rates of adherence play out in real-world set-

**The threshold for evaluating for OSA soon after stroke should be low**

**TABLE 1**

**Randomized trials of positive airway pressure therapy in poststroke patients**

| Authors                      | N (assigned to PAP) | Setting                                   | Diagnostic testing      | Criteria for treatment/type of treatment | Timing of sleep study or start of treatment    | Duration of treatment | Major findings (differences in outcomes between groups)   | P value <sup>a</sup>               |
|------------------------------|---------------------|---|-------------------------|--|--|-----------------------|---|------------------------------------|
| Hsu et al <sup>60</sup>      | 63 (31)             | Stroke rehabilitation unit                | Portable monitor        | AHI ≥ 30<br>ACPAP                        | Around 3 weeks after stroke                    | 8 weeks               | Barthel Index<br>NIH Stroke Scale<br>SF-36 physical / mental  | .17<br>.62<br>.02 / .23            |
| Parra et al <sup>61</sup>    | 30 (15)             | Inpatient neurology                       | Portable monitor        | AHI ≥ 20<br>ACPAP to fixed CPAP          | CPAP days 3–6                                  | 24 months             | 1 month / 24 months<br>Barthel Index > 1 point<br>Rankin Scale > 1 point<br>Canadian Neurologic Scale > 0.5   | .57 / NS<br>.002 / NS<br>.04 / NS  |
| Ryan et al <sup>62</sup>     | 44 (25)             | Inpatient stroke rehabilitation unit      | PSG                     | AHI ≥ 15<br>CPAP titrated by PSG         | Around 3 weeks after stroke                    | 1 month               | Epworth Sleepiness Scale<br>Canadian Neurologic Scale<br>Functional Independence Measure  | < .0001<br>< .001<br>.07           |
| Bravata et al <sup>63</sup>  | 55 (31)             | Inpatient stroke unit                     | PSG                     | No AHI cutoff<br>ACPAP                   | ACPAP started within 48 hours of symptom onset | 1 month               | Improvement in NIH Stroke Scale<br>Vascular events (transient ischemic attack, stroke, myocardial infarction, heart failure, death)                 | .03<br>.31                         |
| Parra et al <sup>64</sup>    | 126 (57)            | Inpatient stroke unit                     | Portable monitor        | AHI ≥ 20<br>ACPAP to fixed CPAP          | CPAP days 3–6                                  | 5 years               | Cardiovascular survival<br>Cardiovascular event-free survival   | .015<br>.059                       |
| Khot et al <sup>65</sup>     | 40 (20)             | Inpatient rehabilitation unit             | Portable monitor or PSG | No AHI cutoff<br>ACPAP or sham ACPAP     | ACPAP around day 10                            | 2 weeks               | Functional Independence Measure-Total<br>Functional Independence Measure-Cognitive<br>Functional Independence Measure-Motor                         | .25<br>.04<br>.42                  |
| Aaronson et al <sup>66</sup> | 36 (20)             | Inpatient stroke rehabilitation unit      | Portable monitor        | AHI ≥ 15<br>CPAP                         | CPAP at 3–4 weeks after stroke                 | 4 weeks               | NIH Stroke Scale<br>Canadian Neurologic Scale<br>Activities of Daily Living / USER<br>Improvement in attention<br>Improvement in executive function | .08<br>.08<br>.11<br>.048<br>.001  |
| Gupta et al <sup>67</sup>    | 70 (34)             | Neurologic inpatient or outpatient clinic | PSG                     | AHI > 15<br>Fixed CPAP to ACPAP          | CPAP around 6–8 weeks after stroke             | 12 months             | Blood pressure<br>New cardiovascular event<br>Barthel Index > 1 point<br>Modified Rankin Scale > 1 point<br>Epworth Sleepiness Scale                | NS<br>.23<br>.96<br>.03<br>< .0001 |

<sup>a</sup>When statistically significant ( $P < .05$ ), the difference favors CPAP.

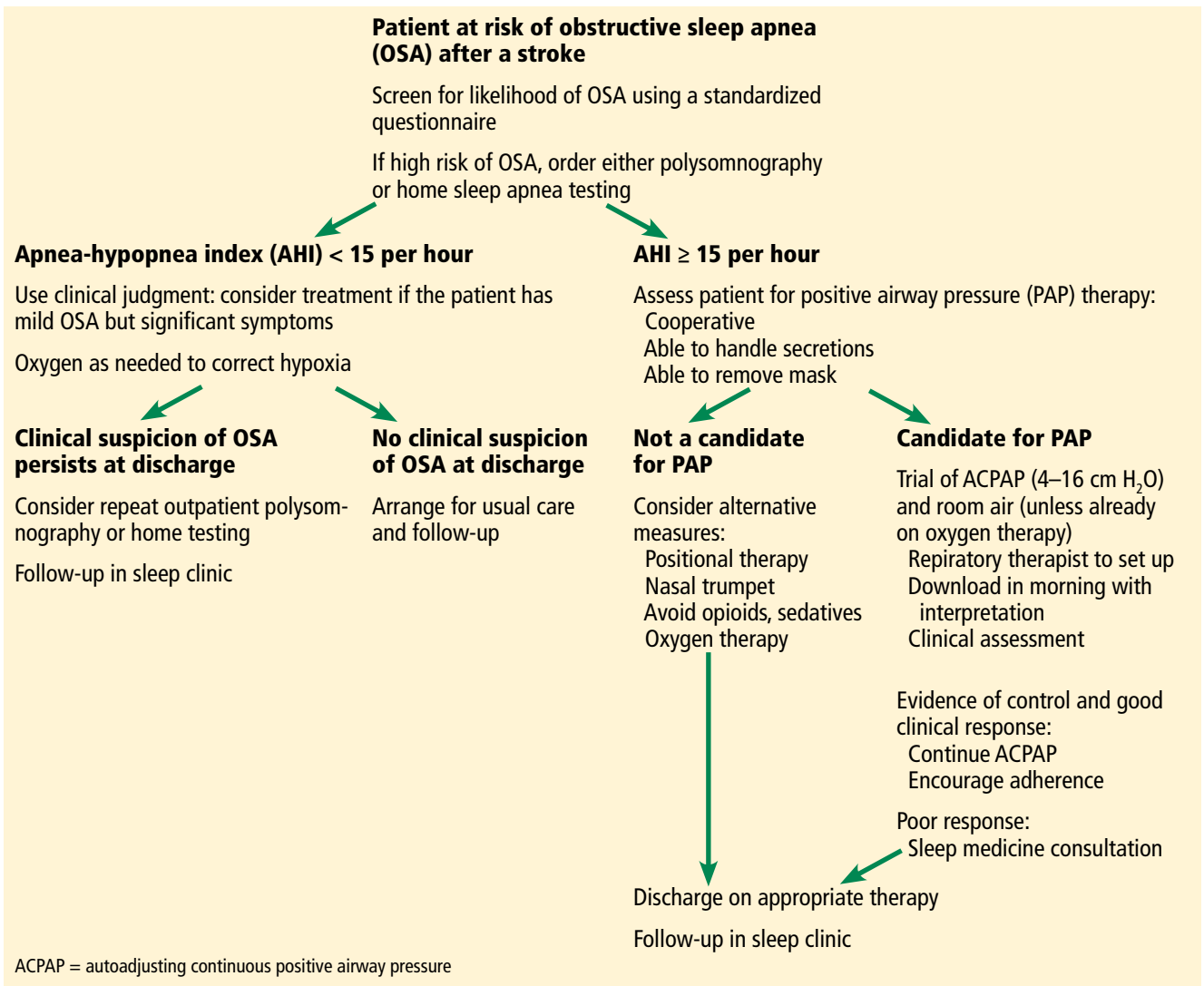
ACPAP = autoadjusting CPAP; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; NIH = National Institutes of Health; NS = nonsignificant; PAP = positive airway pressure; PSG = polysomnography; SF-36 = Short Form 36; USER = Utrecht Scale for Evaluation of Rehabilitation

tings, outside of the controlled environment of a research study, has yet to be determined.

In general, CPAP adherence is affected by claustrophobia, difficulty tolerating a mask, problems with pressure intolerance, irritating air leaks, nasal congestion, and naso-oral dryness. Many such barriers can be overcome

with use of a properly fitted mask, an appropriate pressure setting, heated humidification, nasal sprays (eg, saline, inhaled steroids), and education, encouragement, and reassurance.

After a stroke, additional obstacles may impede the ability to use PAP therapy.<sup>68</sup> Facial paresis (hemi- or bifacial) may make fitting of



**FIGURE 1.** Managing obstructive sleep apnea after stroke.

the mask problematic. Paralysis or weakness of the extremities may limit the ability to adjust or remove a mask. Aphasia can impair communication and understanding of the need to use PAP therapy, and upper-airway problems related to stroke, including dysphagia, may lead to pressure intolerance or risk of aspiration. Finally, a lack of perceived benefit, particularly if the patient does not have daytime sleepiness, may limit motivation.

### Consider alternatives

For patients unlikely to succeed with PAP therapy, there are alternatives. Surgery and oral appliances are not usually realistic options in the setting of recent stroke, but positional therapy, including the use of body

positioners to prevent supine sleep, as well as elevating the head of the bed, may be of some benefit.<sup>69,70</sup> A nasopharyngeal airway stenting device (nasal trumpet) may also be tolerated by some patients.

Avoiding or minimizing sedating medications that may worsen OSA, such as benzodiazepines and opioids, should be considered.<sup>3</sup> Oxygen therapy, while helping to maintain oxygen saturation during sleep, does not prevent airway collapse, and its role for treating OSA in patients after stroke is unclear.

A proposed algorithm for screening, diagnosing, and treating OSA in patients after stroke is presented in **Figure 1**. ■

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