Alternative Therapies for Obstructive Sleep Apnea

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KEYWORDS

• Obstructive sleep apnea • Alternative apnea therapy • Positional therapy • Acupuncture • Hypoglossal nerve stimulation • Didgeridoo playing

KEY POINTS

- Patients are interested in a wide variety of alternative therapies and a common disorder such as obstructive sleep apnea is approached by many as an opportunity to pursue these.
- The search for an alternative to continuous positive airway pressure (CPAP) has produced promising results.
- Some of these alternatives are effective in patients with certain categories of OSA, although further tailoring and refining are required.
- These alternatives should be entertained in selected patients with OSA who are intolerant of CPAP because CPAP is likely to remain first-line therapy in the near future.
- We predict that alternatives to CPAP will become mainstream over the next 2 decades.

INTRODUCTION

Patients are interested and actively involved in alternative medicines and therapies, and many of them do not stay with continuous positive airway pressure (CPAP) therapy over the long term even if they do not lose weight. Compliance with CPAP therapy has been well recognized by researchers and practicing physicians as a common hurdle in the treatment of obstructive sleep apnea (OSA). A wide range of compliance has been reported in the literature, ranging from 46% to 85%.[1] CPAP compliance has also been shown to decrease with time. Abdelghani and colleagues[2] followed 72 patients with OSA started on CPAP for a mean duration of 22 ± 15 months. CPAP compliance was 92% at 6 months, 83% at 12 months, and 59.9% at 3 years. In the compliant patients, the CPAP was used for a mean of 4.5 hours. Studies such as these prompted a search for CPAP alternatives for the treatment of OSA.

This article reviews these alternatives in depth and focuses on studies that measure clinically meaningful outcomes such as apnea/hypopnea index (AHI), oxygen desaturation during sleep, and measured daytime sleepiness such as the Epworth Sleepiness Scale (ESS). Literature that could shed the light onto the pathophysiologic plausibility of these alternatives is also reviewed. In the studies reviewed, continuous variables were usually reported as the mean of the value ± standard deviation or as median with its range (x to y). Categorical variables were usually reported as odds ratios with 95% confidence intervals (CIs). A 2-tailed *P* value was reported with most of these variables.

NASAL RESISTIVE DEVICES

Multiple imaging studies have been done on the upper airway in patients with OSA to evaluate the site of obstruction, its timing in the respiratory

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cycle, and the response to different therapeutic modalities. These imaging modalities include nasopharyngoscopy, fluoroscopy, cephalometric radiography, computed tomography (CT), magnetic resonance imaging, echo imaging, and computer fluid dynamics (CFD).[3,4] Schwab and colleagues[5] used dynamic CT imaging to evaluate the airways of 42 individuals: 15 normal controls, 14 snorers/mildly apneic patients, and 13 patients with OSA with a respiratory disturbance index (RDI) greater than 15 events/h. This study revealed that little airway narrowing occurred during inspiration even in patients with OSA and that the airway narrowed significantly at the end of the expiration, especially in patients with OSA. The investigators explained the absence of obstruction in inspiration despite the negative airway pressure at that time to be secondary to a balancing increase in upper airway dilator muscle activity, and they suspected that expiration was passive such that the loss of positive intraluminal pressure generated by the expired air led to the worst airway narrowing at the end of expiration. These findings prompted the testing of CPAP alternatives to maintain a positive intraluminal pressure at end-expiration to maintain the airway patency.

In a pilot study involving 24 patients with OSA and 6 primary snorers, Colrain and colleagues[6] evaluated the use of an expiratory resistance device (made by Ventus Medical) consisting of 2 nasal valves mounted over a nasal cannula that monitored the airflow. The valves had negligible resistance in inspiration and a resistance of 60 to 90 cm H_2O/s/L at a flow of 100 mL/s during expiration. The device use had a favorable response: average AHI decreased (from 24.8 $\pm$ 22.1 to 14.2 $\pm$ 22.1, P<.001), the oxygen desaturation index (ODI) decreased (from 14.6 $\pm$ 16.9 to 9.9 $\pm$ 15.2, P<.01), and percentage of total sleep time (TST) with snoring decreased (from 26.9% $\pm$ 19% to 9.4% $\pm$ 10.7%, P<.001). The device was well tolerated, with only 2 subjects describing it as very uncomfortable. Only 1 of the 11 patients who had previously used CPAP considered the device to be somewhat less comfortable than CPAP, whereas the rest found CPAP to be much less comfortable than the device.

Rosenthal and colleagues[7] reexamined the same expiratory resistance device on 34 patients with OSA. Patients underwent 4 polysomnograms (PSGs): 1 baseline control PSG and 3 PSGs using the device with 3 different resistances (50, 80, and 110 cm H_2O/s/L). This was followed with a final PSG after 30 days of using the device with the most effective resistance. Twenty-eight patients completed the study protocol and intent-to-treat analysis revealed a decrease in average AHI from 24.5 $\pm$ 23.6 on control PSG to 13.6 $\pm$ 19.6 with the 50 cm H_2O/s/L resistance, 12.5 $\pm$ 18.8 with the 80 cm H_2O/s/L resistance, and 14.4 $\pm$ 19.7 with the 110 cm H_2O/s/L resistance. Thirty days after using the device with the most effective resistance, the final PSG revealed an average AHI of 15.5 $\pm$ 18.9 (P = .001). Also at 30 days, the percentage of sleep time snoring also decreased (from 27.5% $\pm$ 23.2% to 14.6% $\pm$ 20.6%, P = .013), ESS decreased (from 8.7 $\pm$ 4.0 to 6.9 $\pm$ 4.4, P<.001), and the Pittsburgh Sleep Quality Index (PSQI) improved (from 7.4 $\pm$ 3.3 to 6.5 $\pm$ 3.6, P = .042). The device was well tolerated and worn on 94% of the 30 nights.

Further encouraged by these results, Berry and colleagues[8] conducted a prospective, multicenter, sham-controlled, parallel-group, randomized, double-blinded trial on 250 patients with OSA (AHI$\geq$10) using a new expiratory positive airway pressure (EPAP) nasal device. This Ventus Provent was a single-use nasal valve inserted into each nostril and sealed with adhesive. The Provent valve had negligible inspiratory resistance and an expiratory resistance of 80 cm H_2O/s/L at a flow of 100 mL/s. The sham device looked similar to the active device but had negligible inspiratory and expiratory resistance. At 1 week, median AHI with the active device decreased (from 13.8 to 5.0, P<.0001) but not with the sham device (from 11.6 to 11.1, P = not significant [NS]). Similar results were observed at 3 months with median AHI decreasing with the active device (from 14.4 to 5.6, P<.0001) and not with the sham device (from 10.2 to 8.3, P = NS). At 3 months, ESS decreased with both devices: from 9.9 $\pm$ 4.7 to 7.2 $\pm$ 4.2 (P<.0001) in the EPAP group and from 9.6 $\pm$ 4.9 to 8.3 $\pm$ 5.1 (P = .001) in the sham device group. However, the Provent group had a significantly bigger decrease in ESS than the sham group (P = .04). The active device also showed improvement in the ODI and percent TST with oxygen saturations greater than 90%. The Provent success rate (success defined as AHI decrease $\geq$50% or AHI decrease to <10) was 62% at 1 week and 50.7% at 3 months. Reported adherence to Provent was at 88.2% versus 92.3% for the sham device (P = .02).

Long-term use of the Ventus Provent EPAP device was evaluated by Kyger and colleagues[9] in a prospective, single-arm, open-label extension of the AERO trial. Responders from the AERO trial (response defined as AHI decrease $\geq$50% or AHI decrease to <10) who used the device for 4 hours or more per night and 5 nights or more per week were eligible. Forty-one of 51 eligible patients chose to participate and, after 7 early terminations,

34 patients finished the study. Compared with baseline data collected in the AERO trial, the Provent device at 12 months still had a favorable response: median AHI decreased from 15.7 to 4.7 (P<.001), median ODI decreased from 12.6 to 7.6 (P = .08), percent TST snoring decreased by a median of 74.4% (P<.001), and average ESS improved from 11.1 ± 4.2 to 6.0 ± 3.2 (P<.001). The device was reported to be worn on 89.3% of nights. Forty-two percent of all Provent users (17/41) reported adverse events, including difficulty exhaling, nasal discomfort, dry mouth, headache, and insomnia.

Patel and colleagues[10] evaluated the Provent valve in 20 patients with OSA (AHI>5) and found similar results. In the 19 patients who tolerated the device, RDI decreased (from 49 ± 28 to 27 ± 29 events/h, P<.001), with 50% of patients having adequate response (defined as RDI decrease of >50% to <20 events/h). No significant predictor of response could be elucidated.

In another trial, by Walsh and colleagues,[11] 59 patients with OSA (AHI>15 or AHI>10 with OSA symptoms) who had not tolerated CPAP therapy were single-blindedly offered Provent EPAP devices with 2 different resistances (50 cm H_2O/s/L [R50] and 80 cm H_2O/s/L [R80] at a flow of 100 mL/s). Patients were allowed to chose a preferred device after trying both (24 patients chose R50 and 15 patients chose R80) or were assigned a device if they had no preference. Forty-seven patients (80%) tolerated the EPAP trial and completed a screening/baseline PSG (PSG1). Forty-three of these patients met all inclusion criteria and proceeded to get a second PSG (PSG2) to assess the efficacy of the device within 10 days of PSG1. Efficacy was defined as greater than a 50% reduction in AHI from PSG1, or AHI less than 10, or greater than 30% decrease in AHI associated with a decrease in ESS greater than 2 from a baseline less than 12. Twenty-four patients fulfilled the efficacy criteria and proceeded with a third PSG (PSG3) done about 5 weeks after continued use of the device. In these 24 patients, average AHI was 31.9 ± 19.8 at PSG1, 11.0 ± 7.9 at PSG2, and 16.4 ± 12.2 at PSG3 (P<.001 compared with PSG1 and P = .023 compared with PSG2). The investigators attributed the increase in AHI in PSG3 compared with PSG2 to the regression to the mean statistical phenomenon. ESS also improved in this group (from 11.1 ± 5.1 at PSG1 to 8.7 ± 4.4 at PSG3, P = .03). Reported compliance was greater than 92%. Predictors of efficacy were a Mallampati score of less than 4, a lower baseline AHI, and a lower baseline percentage of TST spent with oxygen saturation less than 90%.

EPAP nasal resistive devices show promising results, as shown by the review of the published literature. The mechanism of action has a clear and proven pathophysiologic explanation and its simplicity is appealing. However, these devices are difficult to tailor to the individual patient because they have fixed resistances, and this can explain the partial response in some patients. This partial response could be solved by using a device with variable adjustable resistance in the sleep laboratory to determine the optimal resistance, and then prescribing an EPAP nasal device with a matching resistance.

POSITIONAL THERAPY

The effect of sleep position on the OSA has been well established. Positional OSA has been defined as OSA with AHI in the supine position that is at least double the AHI in a nonsupine position.[12(pp189)]

Oksenberg and colleagues[13] retrospectively reviewed the PSG data of 666 patients diagnosed with OSA (defined as RDI>10) and selected 547 patients (RDI>10, age>20 years, body mass index [BMI] >20 kg/m^2, and >30 minutes of either sleep position) for analysis to compare positional patients (PP) with nonpositional patients (NPP), and 55.9% of patients had positional sleep apnea. Compared with NPP, the PP group were 2 years younger (age, 52.9 vs 54.9 years, P = .02), thinner (BMI, 29.4 vs 31.9 kg/m^2, P = .001), and had milder disease: lower apnea index (AI) (13.7 vs 26.5 events/h, P = .001), lower RDI (27.8 vs 44.0 events/h, P = .001), and higher oxygen saturation (Sa_{O_2}) nadirs (rapid eye movement [REM] sleep, 81.1% vs 72.7%, P = .001; and non-REM [NREM] sleep, 84.7% vs 81.5%, P = .001).

Similar differences between PP and NPP were observed by Soga and colleagues[14] in 31 patient with OSA (AHI>15), notably younger age (43.0 vs 51.6 years), lower AHI (21.1 vs 50.9 events/h), and lower BMI (26.4 vs 28.4 kg/m^2), but none of these differences were statistically significant. This finding could be explained by the small sample size compared with the study by Oksenberg and colleagues[13] mentioned earlier. For the site of obstruction in PP versus NPP, Ravesloot and de Vries[15] performed drug-induced sleep endoscopy (DISE) on 100 patients with OSA and noted a trend toward more obstruction to occur in the base of tongue and epiglottis in PP (P = .058).

Probably the first reported attempt at positional therapy came from the wife of a patient who described in a letter to her doctor how she “sewed a pocket into the back of a T-shirt and inserted a

hollow, light-weight plastic ball" into the pocket, resulting in the resolution of her husband's snoring and daytime sleepiness within about 2 days of use.[16]

Maurer and colleagues[17] tested a vest with a half-cylindrical piece of hard foam in its dorsal part on 12 men with positional OSA and compared the PSGs with the baseline PSGs done the night before. Adequate response was defined as a reduction in AHI of greater than 50% to a value of less than 10 events/h. With the vest, AHI decreased (26.5 ± 12.0 to 7.6 ± 5.11 events/h, $P<.005$), Sa_{O_2} nadir increased (80% ± 7.2% to 85% ± 7.8%, $P<.05$), and percentage of TST with Sa_{O_2} less than 90% decreased (11.7% ± 11.3% to 1.5% ± 2.1%, $P<.005$). Nine patients (75%) had adequate response to the vest.

The vest was again tested by Wenzel and colleagues[18] on 14 patients with positional OSA to assess its efficacy and long-term compliance. The vest use again led to a reduction in AHI (31.3 ± 12.9 to 13.8 ± 9 events/h, $P<.001$), a trend to a higher Sa_{O_2} nadir (82% ± 6.2% to 86.4% ± 4.7%, but P = NS), and a decrease in percentage of TST with Sa_{O_2} less than 90% (8.2% ± 7.1% to 3.8% ± 4.5%, $P<.001$). Only 4 patients (28.6%) reported still using the vest 24 ± 28.8 months later and, in these patients, the ESS decreased (from 8.5 ± 3.2 to 6.5 ± 2.9, $P<.05$). Discomfort was reported to be the reason for the poor compliance.

Oksenberg and colleagues[19] offered a different form of positional therapy, the tennis ball technique (TBT), to 78 patients with positional OSA after the patients declined CPAP therapy. The patients purchased, for US$7.5, a wide cloth belt that had a pocket that was later stuffed with a tennis ball. The belt was worn around the chest with the pocket to the back, thus preventing a supine sleep position. A questionnaire was sent to the patients 6 months after starting the intervention. Fifty patients (64.1%) returned the questionnaire. Nineteen patients (38%) reported continued use of the technique and had better self-reported sleep quality ($P<.005$), improved daytime alertness ($P<.046$), and decreased snoring loudness ($P<.001$). Discomfort was the most common reason behind noncompliance. In the same study, the efficacy of the technique was shown in 12 other patients: AHI decreased (46.5 ± 19.9 vs 17.5 ± 19.4 events/h, $P<.002$) and Sa_{O_2} nadir increased (REM, 81.3% ± 9.9% vs 90.3% ± 4.7%, $P<.009$; and NREM, 85.1% ± 5.6% vs 89.9% ± 3.9%, $P<.009$). Long-term compliance was also studied by Bignold and colleagues,[20] who sent questionnaires to 108 patient 2.5 ± 1.0 years after starting TBT. Sixty-seven patients responded and responders had similar demographic and clinical characteristics to the nonresponders. Only 4 patients (6%) reported continued TBT use.

A slightly modified TBT was also compared with nasal CPAP (nCPAP) in a randomized crossover study of 20 patients with positional OSA (mean AHI, 22.7 ± 12.0). A thoracic antisupine band (TASB) was wrapped around the anterior chest and shoulder, intersecting on the back in the interscapular area at the level of the sixth vertebra where a ball was inserted. One month later, the TASB effectiveness was inferior to CPAP, with mean AHI of 12.0 ± 14.5 with the band versus 4.8 ± 3.9 with nCPAP (P = .02). Successful outcome (defined as AHI<10) was reached in 72% of patients with the TASB versus 89% with nCPAP (P = .004). However, patient-reported adequate adherence to therapy (defined as use for ≥4 h/night on ≥70% of nights) was better for the TASB (95%) than nCPAP (45%), with $P<.001$. There was no significant difference in ESS between the two treatments.[21]

In another study involving 16 patients with positional OSA, Heinzer and colleagues[22] reported a more objective assessment of compliance with a further modification of the TBT. The modified device used a firm plastic piece over the back instead of a ball and added shoulder straps to the belt to prevent sideways movement of the plastic piece. An actigraphic recorder in the device monitored its use and, at 3 months, the device was used 73.7% ± 29.3% of the time for an average of 8.0% ± 2.0 h/night.

Other forms of positional therapy devices have been used. Loord and colleagues[23] used The Positioner on 23 patients with positional OSA (AHI>15 in supine and AHI<5 events/h in lateral position). The device consisted of a vest attached to a board with Velcro fasteners and a pillow placed at the head of the board. The design allowed turning between lateral positions but not the supine position. Five patients could not tolerate the device and 18 patients completed the study. PSGs were done at baseline and at 6.8 ± 3.2 months. Thirteen of the 18 patients had a decrease in AHI with 11 patients (61%) having second AHI less than 10 events/h, with mean AHI decreasing from 21.8 to 14.3 (P = .02). ESS also decreased from 11.8 to 10.2 (P = .02). Another device, the Zzoma Positional Sleeper, was compared with CPAP on 38 patients with positional OSA (nonsupine AHI<5). This device consisted of a backpack-type foam attached over an elastic band that was wrapped around the chest. The foam was bulky and wedge-shaped to secure the patient in a lateral position. With the device, there was no time spent in the supine position.

Median AHI decreased from 11 to 2 events/h with the device and to 0 events/h with CPAP (P<.001). Fifty percent of the patients preferred the device, whereas 34% preferred CPAP and the rest were undecided.[24]

To overcome the poor compliance caused by the discomfort causing frequent awakenings with other devices, Van Maanen and colleagues[25] instead used a small battery-operated vibrating device (3 × 3 × 1 cm) on 30 patients with OSA. The device had a position sensor and vibrations started 10 seconds after the supine position was assumed and increased in intensity until the patient changed position. With the device on, mean AHI decreased (from 27.7 ± 2.4 to 12.8 ± 2.2 events/h, P = .00) with 7 patients (23%) achieving an AHI of fewer than 5 events/h. Percentage of TST in the supine position decreased (40% ± 3.5% to 19.0% ± 4.1%, P = .00) without an increase in the number of awakenings. Encouraged by these results, Van Maanen and colleagues[26] tested the Sleep Position Trainer (SPT; a small device in a pocket of a neoprene strap worn around the chest) on 31 patients with positional OSA. The device had a USB port to communicate more than 90 days' worth of position data to a computer and to charge the device. With the device, median AHI decreased (from 16.4 to 5.2 events/h, P<.001), Sa_{O_2} nadir increased (85.4 ± 4.1 to 88.4 ± 3.6, P<.001), and median ESS score decreased (from 11 to 9, P = .004). There was no increase in awakenings and median compliance with the device use was 92.7% (range, 62%–100%).[26] The SPT (by NightBalance BV) is now available by prescription in some European countries.[27]

An adaptation of the SPT is now available as an Android phone application under the name of Apnea Sleep Position Trailer, which records the sleep position, causes the phone to vibrate if the supine position is detected, and sounds an alarm if the person does not respond by changing position.[28] The application can be downloaded from Google Play for US$2.60.[29] The Android phone is then placed in a sport belt such as the Tune Belt (by Tune Belt Inc), which is available for less than US$25.[30]

The efficacy of positional therapy for positional OSA has been shown and, until recently, patient discomfort has been the biggest obstacle to good compliance. With the advent of smarter devices, it seems the days of the bulky devices are numbered. Positional therapy device development is another example of market innovation, such as smart phone applications, bypassing the lengthy approval process of regulatory bureaucracy.

SNORE PILLOWS

In the search for alternatives to CPAP for treatment of OSA, readjustment of the head position during sleep was attempted to increase the airway caliber in the hope of preventing the obstructive apneas.

Kushida and colleagues[31] tested PillowPositive, a cervical pillow that promotes head extension, on 18 patients with mild to moderate OSA. Baseline electromyogram (EMG) was done on 2 nights, followed by a 5-night adjustment period sleeping with the cervical pillow, and then repeat EMG over 2 nights was performed with the cervical pillow. The use of the cervical pillow resulted in a reduction in the mean RDI (from 17.8 ± 6.8 to 13.6 ± 7.3, P = .003) but made no significant difference in obstructive events, oxygen saturation nadir, or subjective sleep quality.[31]

SONA Pillow, a pillow designed to prevent supine sleep positions, was tested on 22 patients with OSA. In the subgroup of patients with mild (N = 11, RDI 5–19) and moderate (N = 8, RDI 20–40) OSA, the pillow use reduced the average RDI by 17 to less than 5 (P = .001), increased Sa_{O_2} (P = .004), and decreased or eliminated snoring (P = .017).[32] Svaticova and colleagues[33] also tried the SONA Pillow on 18 patients with recent stroke (within 14 days) and OSA in a randomized, controlled, crossover study. The pillow use resulted in a reduction in the median AHI from 39 (range 21–54) to 27 (range 22–47, P = .011). At 3 months, 4 of the 9 patients randomized to the pillow (44%) were still using the pillow every night or most nights.

A different pillow designed to achieve an elevated posture was tested on 14 patients with OSA in a randomized crossover study. The shoulder-head elevation pillow (SHEP), a foam wedge with 60° inclination, was compared with nCPAP and was significantly inferior: mean AHI decreased from 27 ± 12 to 21 ± 17 with the SHEP versus 5 ± 3 with nCPAP (P = .008 comparing the two treatments).[34]

It is difficult to consider the aforementioned pillows as CPAP alternatives, but there is probably a role for them as adjunct treatments for OSA.

HYPOGLOSSAL NERVE STIMULATION

Multiple studies examined the site of obstruction in the upper airway in patients with OSA during both wakefulness and sleep. Different methods were used including physiologic measurements of pressure and resistance, flextube reflectometry using acoustic reflection, fiberoptic visualization, and different imaging modalities including cephalometric roentgenograms, fluoroscopy, CT, and

magnetic resonance imaging.[35] Patients had one or more site of obstruction with the retropalatal site dominating followed by the retrolingual site, with the site of obstruction affected by sleep phase but not by sleep position.[36]

Submental electric stimulation was initially attempted and decreased AHI, longest apnea duration, lowest Sa_{O_2}, and time spent with Sa_{O_2} less than 85%.[37,38] Videoradiography during submental electric stimulation in a patient showed a forward movement of the tongue breaking the obstructive apnea without evident arousal of the patient.[39] In a subsequent study of 8 patients with positional and nonpositional OSA, submental and transhyoidal transcutaneous electric stimulation led to protrusion of the tongue with increased cross-sectional area of the orohypopharyngeal segment of the upper airway, but it failed to decrease the AHI. In this study, a cutoff of AHI greater than or equal to 40/h was used to define OSA.[40]

After more mixed results obtained with submental stimulation,[41,42] Schwartz and colleagues[43] tried soft palate electric stimulation on 7 patients and successfully treated snoring but not OSA. Selective stimulation of the genioglossus muscle was later shown to improve airway patency.[44] Eisele and colleagues[45] then showed that stimulation of the branch of the hypoglossal nerve, which contracts the genioglossus muscle, produced protrusion and contralateral deviation of the tongue, whereas stimulating the nerve led to retrusion and ipsilateral deviation of the tongue. The genioglossus muscle is an extrinsic muscle of the tongue that attaches to the superior genial tubercle of the mandible.[46] Although this muscle was originally thought to be the single tongue protrusor muscle, tongue protrusion is more likely produced by the combined efforts of muscle units from different tongue muscles.[47] The complexity of the tongue functional anatomy can explain the conflicting results obtained with submental stimulation.

Schwartz and colleagues[48] implanted the Medtronic Inspire I stimulating system, a unilateral hypoglossal nerve–stimulating device into 8 patients with OSA. The device consisted of a half-cuff electrode placed around the hypoglossal nerve branch innervating the genioglossus muscle of the tongue, an intrathoracic pressure sensor drilled through the superior manubrium, and an implantable pulse generator placed in the infraclavicular subcutaneous pocket. After the device was activated, mean AHI (measured in episodes per hour) decreased during NREM sleep (from 52 $\pm$ 20.4 to 22.6 $\pm$ 12.1, $P<.001$) and REM sleep (from 48.2 $\pm$ 30.5 to 16.6 $\pm$ 17.1, $P<.001$). Mean low Sa_{O_2} also improved during NREM sleep (from 89.7% $\pm$ 2.9% to 91.7% $\pm$ 2.0%, $P<.5$) and REM sleep (from 88.7% $\pm$ 6.5 % to 91.6% $\pm$ 2.2%) after the device activation.

A different hypoglossal nerve stimulation device, the Apnex Medical Hypoglossal Nerve Stimulation (HGNS) system was used by Eastwood and colleagues[49] in a multicenter trial on 21 patients with moderate to severe OSA who failed multiple attempts of CPAP implementation. In addition to AHI between 20 and 100/h with at least an AHI greater than 15/h during NREM sleep, a hypopnea-driven AHI with hypopneas constituting greater than or equal to 80% of the events and a BMI less than or equal to 40 kg/m^2 were among the inclusion criteria. The new device had a stimulating lead, which was placed on the hypoglossal nerve distal to the branches that innervate the retrusor muscles of the tongue. Intraoperative fluoroscopy was used to verify proper placement yielding the desired tongue protrusion with stimulation. This stimulator lead was then tunneled under the skin and attached to an infraclavicularly implanted neurotransmitter that was also attached to 2 sensing leads that were tunneled distally along each costal margin. The sensors measured changes in bioimpedence to signal the beginning of inspiration. The patient controlled the device with a handheld controller. Patients used the device 89% $\pm$ 15% of nights for 5.8 $\pm$ 1.6 h/night. PSGs done at 6 months for 19 of these patients showed a decrease in AHI (from 43.1 $\pm$ 17.5 to 19.5 $\pm$ 16.7 events/h, $P<.001$) and in arousal index (from 43.8 $\pm$ 19.5 to 11.0 $\pm$ 13.8 events/h, $P<.001$). Patients also had symptomatic improvement with ESS decreasing from 12.1 $\pm$ 4.7 to 8.1 $\pm$ 4.4 with $P<.001$ over the same time period.

The Inspire II Upper Airway Stimulation (UAS) by Inspire Medical Systems, the second generation of the system studied by Schwartz and colleagues,[48] was used in a 2-part open prospective study done by Van de Heyning and colleagues.[50] The new system had the pressure-sensing lead placed in the fourth intercostal space instead of being drilled through the superior manubrium and the stimulating lead embedded in cuffs wrapping around the main hypoglossal nerve in part 1 and around the medial branch of the nerve that innervates the genioglossus muscle in part 2 of the study. In part 1 of the study, 22 patients with OSA (with AHI$\geq$25 and BMI<35 kg/m^2) who failed or could not tolerate CPAP therapy received the device, with 20 of them completing the study (1 lost to follow-up and 1 had a device-related infection). Seven of these patients underwent a DISE procedure to evaluate the site, degree, and pattern of

the upper airway collapse during sleep. The subjects were evaluated with PSG at baseline, 2, 4, and 6 months. The patients as a group did not have a significant improvement in AHI at 6 months. The patients were then divided into responders (AHI decreasing more than 50% to less than 20 events/h at 6 months) and nonresponders, and their baseline characteristics were compared. The responders had a lower baseline AHI (26.1 ± 5.0 vs 51.1 ± 16.8 events/h, $P<.01$) and a lower baseline BMI (27.8 ± 1.8 vs 30.7 ± 2.6 kg/m^2, $P<.05$). Analysis of the results of the DISE procedure that had been done on 7 of the 20 patients showed that the 3 patients who had complete concentric collapse at the level of the soft palate were nonresponders, whereas the other 4 patients were responders. Based on these results, the second part of the study inclusion criteria were adjusted to favor responders: BMI less than or equal to 32 kg/m^2, AHI between 20 and 50 events/h, and the absence of complete collapse at the level of the soft palate on DISE. A total of 9 patients were enrolled in this part, with 8 patients reaching the 6-month follow-up and included in the data analysis (1 patient excluded because of inadequate tongue response). As expected, this group was responsive to the intervention, with decreased AHI (28.9 ± 9.8 to 10 ± 11 events/h, $P<.01$) and arousal index (22.7 ± 8.2, $P<.01$). Only 1 patient was a nonresponder. Among all 28 subjects in both parts of the study, ESS significantly improved with intervention (11 ± 5.0 to 7.6 ± 4.3, $P<.01$).

The longest follow-up was 1 year, reported by Mwenge and colleagues.[51] In this pilot study, 14 patients with OSA and having intolerance to CPAP therapy were included. The aura6000 by ImThera Medical was successfully implanted in 13 of the 14 patients. This device has no sensor limb and consists of an implanted pulse generator (IPG) and a 6-electrode stimulator lead ending with a cuff that encircles the hypoglossal nerve near the middle tendon of the digastric muscle. Another distinctive feature of this device is the transcutaneously rechargeable IPG battery. At 12 months, the AHI decreased (from 45 ± 18 to 21 ± 17 events/h, $P<.001$) and so did the arousal index (from 37 ± 13 to 25 ± 14, $P<.001$). There was also an insignificant decrease in ESS (from 11 ± 7 to 8 ± 4, $P = .09$).

Encouraged by these results, 6 trials are ongoing using the 3 devices mentioned earlier (clinicaltrials.gov).[52] To date, none of these devices is approved by the US Food and Drug Administration for routine patient use in the United States, but the Apnex HGNS system has been approved for sale in Europe.[53]

ACUPUNCTURE

Acupuncture has been a mainstay of traditional Chinese medicine for thousands of years. In the West, the practice has been an integral part of alternative therapies for various diseases. Most studies comparing acupuncture with sham procedures for treatment for OSA have been reported in Chinese. The targeted body areas were in the head and neck, most notably the ear.

In an animal study, Janssens and colleagues[54] reported performing acupuncture on 84 different animals in various forms of respiratory depression. The acupuncture procedure involved mainly needling of the philtrum point VG 26 (Jen Chung), which is located in the midline of the nasolabial cleft or philtrum at the level of the lower canthus of the nostril, by inserting a needle of 25 to 28 gauge to a depth of 10 to 20 mm. Sixty nine animals (48 dogs and 21 cats) were in respiratory depression or apnea induced by general anesthesia. Respiration was restored to normal or near normal in all of these animals within 10 to 30 seconds of the needle insertion. Acupuncture also revived 3 of 7 cats and dogs with anesthesia-induced cardiopulmonary arrest after 4 to 10 minutes of needle stimulation. Despite this being an animal study, this report shows the potential of acupuncture in the stimulation of breathing.

In a study on 45 patients with sleep apnea syndrome, Wang and colleagues[55] randomly assigned 30 patients to auricular plaster therapy, a form of auricular acupuncture, and compared them with 15 patients in a control group receiving vitamin C as placebo. Statistically significant response was noted in the treatment group with improvement in AHI (from 72.4 ± 7.9 to 59.2 ± 10.6 events/h, $P<.01$) and in minimum blood oxygen saturation (from 73.3% ± 4.8% to 77.7% ± 3.8%, $P<.01$). No difference was seen in the placebo group.

In a randomized, single-blinded, placebo-controlled trial by Freire and colleagues,[56] 36 patients were randomized to 3 arms with 12 patients in each arm: a therapeutic acupuncture group, a sham acupuncture group, and a control group. The patients in the treatment group received needles in multiple acupoints in the head, face, neck, wrists, hands, legs, and ankles, whereas the sham group received needle insertions in nonacupoints. Patients in the treatment and the sham acupuncture groups received a total of 10 weekly sessions. All patients had OSA diagnosed on PSG with an AHI greater than 15/h and less than 30/h. Only 26 subjects completed the study: 10 in the treatment arm, 9 in the sham arm, and 7 in the control

arm. Of the 10 patients not completing the study, 7 were excluded after randomization because of long-distance travel. Treatment was associated with improvement in ESS from 11.1 ± 3.3 to 7.5 ± 3 with P = .29 and AHI from 19.9 ± 4.1 to 10.1 ± 5.6 with P = .005. No significant change in ESS or AHI occurred in the sham or control groups. Freire and colleagues[57] later showed an immediate effect of manual acupuncture (MA) and electroacupuncture (EA) on AHI in a study involving 40 patients with moderate OSA with Apnea Hypopnea Index (AHIs) between 15 and 30/h. The patients were randomly assigned to 4 groups: MA (n = 10), EA 10 Hz (n = 10), EA 2 Hz (n = 10), and control groups. Compared with the control group, AHI decreased after MA (from 21.9 ± 8.3 to 11.2 ± 5.5, P = .34) and EA 10 Hz (from 20.6 ± 5.6 to 9.95 ± 5.1, P = .01).

Concerns have been raised about the apparent success of acupuncture, especially with the small sample sizes in the studies discussed earlier, especially in the light of the availability of more established treatments such as CPAP.[58] Nevertheless, it is possible to imagine a scenario in which the physician feels obliged to offer alternative medicine approaches such as acupuncture to the patient who fails or refuses conventional medical therapy.

SPEECH EXERCISES

Twenty or more upper airway muscles, including muscles in the soft palate, tongue, and pharynx, play a major role in keeping the upper airway patent.[59] Exercise to strengthen these muscles may help in the treatment of OSA. In a recent trial, 39 patients with moderate OSA were randomized to 3 months of daily oropharyngeal exercises (involving the tongue, soft palate, and lateral pharyngeal wall) or a daily 30 minutes of deep breathing through the nose (control group). The exercises were taught in weekly 30-minute sessions. In the exercise group (N = 16), there was a decrease in AHI (from 22.4 ± 4.8 to 13.7 ± 8.5, P<.05), a decrease in ESS (from 14 ± 5 to 8 ± 6, P = .006), and decrease in neck circumference (from 39.6 ± 3.6 to 38.5 ± 4.0 cm, P<.05). Snoring intensity and frequency were also significantly reduced. No improvement occurred in the control group (N = 15). Compliance with the exercises was 84% and noncompliant patients were excluded from the study.[60]

The reproducibility of these results in a typical clinical practice is difficult to ascertain, but the speech therapy was not too intensive and patient compliance was encouraging. The postintervention AHI, although reduced, did not normalize. The short duration of the study also questions whether these results can be maintained in the long term. Despite these limitations, speech exercises compare well with other CPAP alternatives and can be a viable option for the motivated patient who is intolerant of CPAP.

MUSICAL INSTRUMENTS

A didgeridoo instructor noted that he and some of his students had decreased daytime somnolence after using the instrument for several months, which prompted Puhan and colleagues[61] to test the instrument on 25 patients with moderate OSA (AHI between 15 and 30) in a randomized controlled trial. Patients in the intervention group (N = 14) received didgeridoo lessons from the instructor and practiced at home for 4 months. They practiced for an average 5.9 ± 0.86 days/wk for 25.3 ± 3.4 minutes. Compared with the control group (N = 11), the didgeridoo group had lower ESS (−3.0 [95% CI, −5.7 to −0.3], P = .03) and lower average AHI (−6.2 [95% CI, −12.3 to −0.1], P = .05) but no difference in sleep quality.

Looking for epidemiologic evidence linking OSA risk and playing wind musical instruments, Brown and colleagues[62] studied the members of the International Conference of Symphony and Opera Musicians (ICSOM). The ICSOM has 4300 active members and e-mail addresses of 3665 of them. The Berlin questionnaire assessing the OSA risk was sent via e-mail and 1111 musicians(30%) responded. There was no difference between musicians playing wind versus nonwind instruments with regard to OSA risk after adjusting for age, sex, and BMI.

Ward and colleagues[63] examined the possible epidemiologic evidence connecting OSA with playing wind instruments to establish whether the type of wind instrument made a difference. A national sample of 906 active musicians was surveyed, again using the Berlin questionnaire, to assess their risk of OSA. After correcting for BMI, playing a double-reed instrument was associated with lower risk of OSA with an odds ratio of 0.508 (95% CI 0.261–0.991, P = .047). Among musicians playing double-reed instruments, the OSA risk was also lower with more hours per week of instrument playing: 16.5 ± 1.2 h/wk in the low-risk musicians versus 9.1 ± 2.7 h/wk in musicians with the high OSA risk.

From the literature reviewed, it is clear that at least some wind instrument playing is associated with lower OSA risk and severity but the effect on AHI is modest and further studies are needed

before such therapies can be offered as viable alternatives to CPAP therapy.

NASAL CANNULAS

A few studies have evaluated nasal cannulas in an attempt to find less burdensome alternatives to CPAP therapy.

In one of the earlier studies, Wilhoit and colleagues[64] examined the effect of using a high-flow nasal cannula (NFLOW) in 13 patients with OSA. The new device was called NFLOW and consisted of 2 fused tubes that split at the patient end in a Y shape with the two tips covered with ear wax, fitted into the nostrils, and then secured in place with an elastic band around the head. The other end of the cannula was attached to an unheated humidifier that was in turn attached to an air compressor. The flow was started at 20 L/min then increased until the obstructive apneas resolved or became rare. PSG findings with the cannula on were compared with a PSG done the night before. Four patients could not tolerate the high flow but 9 patients were able to use the cannula through the night with significant improvement of their desaturation indices: number of desaturations greater than 4% per hour and the average desaturation. Flow rates between 30 and 60 L/min were required to control the obstructive apneas. Nasal airway pressure was recorded and ranged from 1.2 to 13.2 cm H_2O on the lower end to between 7 and 20 cm H_2O on the upper end. The AHI of the group was not reported.[64]

A different and simpler nasal cannula was used in a study by McGinley and colleagues[65] in 11 adult patients with OSA. This cannula consisted of 2 fused tubes that were split to fit around the ears and the ends fused again at the nares with the nasal prongs inserted into the open nostril. This cannula was designed to decrease the noise generated by high flows (as high as 20 L/min) that were generated by the attached air compressor. The patients underwent flow titration at 0, 10, and 20 L/min in the first night and all required 20 L/min flow to relieve the airway obstruction. Patients then had PSGs done on separate nights with and without nasal insufflation at 20 L/min. AHI decreased in all patients, with the average AHI for the group decreasing from 28 $\pm$ 5 to 10 $\pm$ 3 events/h, $P<.01$. This finding represents a decrease in disordered breathing related arousals (18 $\pm$ 4 to 8 $\pm$ 2 events/h, $P<.01$) without an increase in spontaneous arousals (3 $\pm$ 1 to 3 $\pm$ 1, $P = .65$).

McGinley and colleagues[66] later showed similar benefits of the high-flow nasal cannula on 12 children (aged 10 $\pm$ 1 years; BMI 35 $\pm$ 14 kg/m^2) with OSA. Treatment with nasal insufflation (TNI) at 20 L/min was performed on one night and compared with no TNI on another night. With TNI, AHI significantly decreased (11 $\pm$ 3 vs 5 $\pm$ 2 events/h, $P<.01$). The effect of TNI was then compared with CPAP titration done earlier on 10 of the 12 patients. Two of these 10 patients (both with severe OSA with AHI>20 events/h) had a suboptimal AHI with TNI (1 required a CPAP of 20 cm H_2O and 1 could tolerate neither CPAP nor TNI). In the remaining 8 children, TNI was not inferior to CPAP (AHI 2 $\pm$ 1 vs 1 $\pm$ 1 events/h).

In an attempt to find predictors of response to TNI in OSA, Nilius and colleagues[67] studied 56 carefully selected patients with sleep-disordered breathing (SDB). Patients had to have an RDI greater than 5 events/h, have excessive daytime sleepiness, be eligible for but not on CPAP therapy, and have a CPAP pressure requirement that was less that the median pressure of each sleep laboratory (range 8–11 cm H_2O) on CPAP titration study. TNI was started at 10 L/min for comfort and automatically gradually increased to 20 L/min over 5 to 10 minutes. Response was defined as greater than or equal to 50% decrease in respiratory events with RDI less than 10 events/h. Only 3 patients (5%) had a predominance of respiratory effort–related arousals (RERA). TNI decreased RDI in the group (from 22.6 $\pm$ 15.6 to 17.2 $\pm$ 13.2 events/h, $P<.01$) but only 27% reached a therapeutic RDI. Neither the baseline RDI nor the previously prescribed CPAP pressure predicted response. Patients with a predominance of RERAs or hypopneas had a more favorable response to TNI than patients with apnea-predominant disease. None of the 8 patients who had greater than 10% central apneas at baseline responded to TNI.

A meta-analysis of 2343 patients with stroke or transient ischemic attack documented SDB with AHI greater than 5 events/h to be very frequent (72% of patients), with 38% having an AHI greater than 20 events/h. The SDB in this population is mainly obstructive with central apnea predominating in only 7% of patients.[68] Driven by the low compliance with CPAP in these patients, Haba-Rubio and colleagues[69] tried TNI with a flow of 18 L/min in 10 patients with strokes with moderate to severe SDB. TNI was tolerated in all patients, with a favorable response on AHI in 9 of them (group AHI from 40.4 $\pm$ 25.7 to 30.8 $\pm$ 25.7 events/h, $P<.001$). Martinez-Garcia and colleagues[70] showed higher adjusted mortality in patients with strokes who had AHIs greater than 20 events/h and were CPAP intolerant compared with patients with AHI less than 20 events/h, with a hazard ratio (HR) of 2.69 (95% CI 1.32–5.61, $P<.05$). In the same study, mortality was similar

in CPAP-treated patients with AHIs greater than 20 events/h, those with AHI less than 20 events/h, and patients with stroke who were free of OSA.[70]

Taking these findings into account, it is reasonable to try TNI in CPAP-intolerant patients with OSA, especially if their OSAs are hypopnea predominant and they are free of any significant central apneas. However, no significant benefit is expected with TNI if the decrease in AHI is modest. In such patients, other alternatives to CPAP should be sought.

NASAL STRIPS

The role of the nose in OSA has been extensively studied. This article first reviews the studies that were designed to discern the relationship, if any, between nasal resistance and OSA, and it then examines nasal-focused therapies targeting OSA.

Early work by Blakley and Mahowald[71] examined the effect of increased nasal resistance on the severity of OSA. The hypothesis was that increased nasal resistance resulted in larger negative pressure in the nasopharynx to achieve adequate flow of air through the nose in inspiration. Such a larger negative nasopharyngeal pressure was suspected to lead to increased collapsibility to the upper airway, precipitating or worsening OSA. The study enrolled 53 men with snoring undergoing PSG to evaluate for OSA, in addition to 37 healthy volunteers with similar weight, and anterior mask rhinomanometry was performed on all the subjects. The whole group had a higher average nasal resistance than the control subgroup (0.57 $\pm$ 0.91 vs 0.34 $\pm$ 0.13 Pa/cm^3/s, P = .01). Linear regression in 26 subjects who were diagnosed with OSA showed that nasal resistance had no relationship with AI or with the nadir of oxygen desaturation.[71]

In another study by Atkins and colleagues,[72] 71 patients with OSA (AHI>15 events/h) and 70 antisocial snorers (ASS) (AHI<15 events/h) underwent anterior rhinomanometry measuring combined nasal resistance (CNR) and highest unilateral nasal resistance (HUNR) measured during wakefulness in a sitting position. CNR was increased in 5 of the OSA group and in 4 of the ASS group, whereas HUNR was increased in 10 of the patients with OSA and 11 of the ASS group. There was no difference in either CNR or HUNR between the two groups. There was no correlation between AHI and CNR or HUNR in either group. Miljeteig and colleagues[73] found evidence of nasal obstruction in only 4 of 54 patients with OSA and concluded that nasal obstruction was not a major contributor to OSA. The presence of unilateral or bilateral nasal obstruction had no effect on apnea or snoring indices in an earlier study of 683 patients with snoring and suspected OSA referred to an otolaryngology clinic.

Several studies to evaluate the effect of nasal dilators were conducted. Höijer and colleagues[74] evaluated the effect of Nazovent, a plastic nasal dilator inserted into the nares, in 10 patients with snoring or witnessed apneas. PSGs revealed OSA (AHI $\geq$ 5 events/h) in 7 patients. Nasal flow increased with the device in all patients (0.7 L/s with a range of 0.55–0.81 L/s to 0.81 L/s with a range of 0.61–0.98 L/s, P = .02). The average AI in events per hour) for the group decreased (from 18 with a range of 1.8–60 to 6.4 with a range of 1.3–15, P = .08) and the minimum overnight oxygen saturation (Sa_{O_2}) increased (from 78% with a range of 68%–89% to 84% with a range of 76% to 88%, P = .03). However, there was no significant correlation between the degree of improvement in nasal flow (measured during wakefulness in a sitting position) and the improvements in AI or in minimum Sa_{O_2}. Snoring noise also decreased.

The Breathe Right external nasal plaster (NP) was evaluated in another study by Wenzel and colleagues[75] involving 50 patients. The patients were divided into group A, with 30 patients who had OSA (AI>10/h), and group B, with 20 snorers without OSA. Patients underwent initial PSG then cardiorespiratory polygraphy on the following 2 nights. Apart from subjective improvement in nasal breathing, the nasal plaster had neither a significant effect on AI in group A (AI was 29.1 $\pm$ 23.7 without and 26.5 $\pm$ 23.7 with the NP) nor an effect on the snoring index (SI) in group B (SI was 22.2 $\pm$ 7.3 snores/h without NP vs 25.7 $\pm$ 9.4 snores/h with NP). 90% of the patients in group A had unchanged daytime sleepiness scores but 33% of them reported better sleep quality.

Gosepath and colleagues[76] reported another trial of Breathe Right external nasal strips on 26 patients with OSA and snoring who had RDIs greater than 10 events/h. Nineteen of the 26 patients had reductions in RDI with the use of the strips. Predictors of response were nasal turbinate hypertrophy/septal deviation with or without allergic rhinitis, none or mild pharyngeal obstruction, and age less than 55 years. The positive result in this group of patients cannot be extrapolated to typical patients with OSA in whom the site of obstruction is mainly pharyngeal, in the retropalatal and retroglossal regions.[77]

A dichotomous effect of Breathe Right external nasal dilators was reported by Djupesland and colleagues[78] in 18 heavy snorers without severe OSA (defined as snoring >25% of the night and AHI<26/h). After sleeping for a week with the

active nasal strip, PSG was done on the first night with the active strip and then repeated the next night with a placebo strip. In the subgroup of 6 patients who were habitual snorers with severe morning nasal obstruction (AHI<10 and combined minimal cross-sectional area [TMCA] <0.6 cm^2), the dilator showed a trend to increasing minimum sleep Sa_{O_2} (from 89% [95% CI 84.5–92.6] to 93% [95% CI 89.7–96.9], P = .06) and a trend to improving AHI (from 7.4 [95% CI 3.9–10.9] to 5.4 [2.3–8.5], P = .06). In contrast, in the subgroup with TMCA greater than 0.6 cm^2, the active nasal strip led to worsening AHI (from 9.4 [95% CI 5.9–12.9] to 15.2 [95% CI 11.6–18.7], P<.05). Duration and intensity of snoring remained unchanged in either subgroup but subjective evaluation of sleep quality improved.

With these results in mind, there is a lack of evidence for any meaningful benefit for nasal dilators in patients with OSA. Subjective improvement in sleep quality was evident in some studies,[75,78,79] and this suggests a role for the strips in selected patients as an adjunct therapy but not an alternative therapy.

DIAPHRAGMATIC PACING

Diaphragm pacing has been a well established treatment of central hypoventilation and high quadriplegia.[80–82] Upper airway obstruction complicating diaphragm pacing has been well documented. In 1981, Hyland and colleagues[83] reported a case of primary alveolar hypoventilation without OSA that developed OSA after diaphragmatic pacing was initiated. The investigators attributed the obstruction to the loss of the normal temporal coordination of diaphragmatic and abductor upper airway muscle activity with diaphragmatic pacing. Upper airway obstruction was also described in a pediatric diaphragmatic pacing series and the negative airway pressure generated by the pacing was suspected to be contributing to the upper airway obstruction.[84] In a report detailing a 10-year experience with diaphragmatic pacing, Le Pimpec-Barthes and colleagues[85] discussed their reluctance to offer tracheostomy removal to their patients because of the fear of obstructive apneas.

Based on these reports, there is no role for diaphragmatic pacing for the treatment of OSA.

SUMMARY

Patients are interested in a wide variety of alternative therapies and a common disorder such as OSA is approached by many as an opportunity to pursue these. The search for a CPAP alternative has produced some promising results, as discussed in this article. Some of these alternatives are effective in certain categories of OSA, although further tailoring and refining are required. These alternatives should be entertained in selected patients with OSA who are intolerant of CPAP because CPAP is likely to remain first-line therapy in the near future. However, we predict that alternatives to CPAP will become mainstream over the next 2 decades.

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