Making Sense of the Noise: Toward Rational Treatment for Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) affects an estimated 936 million adults 30–69 years old worldwide, with approximately 425 million adults experiencing moderate to severe disease (1). In the United States, conservative estimates suggest that 6% of women and 13% of men have clinically significant OSA, which is defined as an apnea–hypopnea index (AHI) of 15 events/h or greater (2). OSA has major neurocognitive and cardiovascular sequelae, but optimal treatment can be challenging.

Numerous published studies support the roles of positive airway pressure (PAP) therapy, upper airway surgery, mandibular repositioning devices, hypoglossal nerve stimulation, and major weight loss to treat adult OSA. One large database study showed that 70–87% of patients with OSA who start PAP therapy met the Medicare criteria for PAP adherence for 30 of the first 90 days, with the higher proportion for those who chose to use active engagement technology (3). However, another large study found that 39–49% of patients with OSA consistently met the Medicare criteria for PAP adherence at 6 months, suggesting the need for alternative treatments (4). Upper airway surgery has also achieved beneficial outcomes in selected patients, particularly because adherence is not required (5, 6). Mandibular repositioning appliances have similar clinical outcomes to PAP in high-quality systematic reviews (7, 8). Hypoglossal nerve stimulation has also demonstrated substantial improvement in OSA in carefully selected patients (9). Likewise, in patients with class II or III obesity, major weight loss provided by bariatric surgery reduces OSA severity (10). However, all of these therapies have limitations related to efficacy, adherence, or both. Questions remain regarding optimal OSA therapy for individual patients. Ongoing rigorous research is needed to improve treatment outcomes.

In this environment of uncertainty, there has been a recent surge in the number of alternative therapies that have been proposed and marketed for adults with OSA. In some cases, interventions are developed and marketed for snoring, with practitioners or patients assuming effectiveness in OSA. Our field is concerned about the potential harm that comes from aggressive marketing that creates unrealistic expectations because many patients are eager or even desperate for alternative therapies. The purpose of this review is to evaluate the scientific basis for considering emerging therapies as treatments for adult OSA. A PubMed search using generic and brand names of products or approaches was supplemented by searching relevant company websites and, in some cases, contacting proponents of specific therapies.

What Is the Evidence?

Although we are strong proponents of innovative therapies and approaches, we are concerned that many of the therapies that we reviewed lack published, scientifically rigorous data and that some have no independent published studies. Table 1 presents the potential alternative therapies and published literature, excluding individual case reports

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Table 1. Proposed Alternative Therapies for Obstructive Sleep Apnea in Adults

Proposed Treatment	Proposed Mechanism of Action	Evidence Source*
Pillows	Promotes favorable head and/or body position	None
Pillow inserts	Moves pillow when detecting snoring	None
Positional therapy (night balance, night shift, slumberBump, etc.)	Promotes nonsupine body position	(14–19, 60)
Nasal valve dilators (breathe right, mute, sinus cones, latera, and vivaer)	Opens the nasal valve	None
Mouth closure (chin straps and tape)	Converts oral to nasal breathing	(21)
Nasal expiratory positive airway pressure (Provent)	Produces positive pressure during expiration with a nasal resistance valve	(25–30)
Oral expiratory positive airway pressure (Oventus; custom-made device)	Produces positive pressure during expiration with an oral resistance valve	(31)
Oral pressure therapy (Winx)	Applies suction to the soft palate to maintain an anterior position	(32)
Continuous negative external pressure	Applies negative pressure to cervical soft tissues	(33)
Didgeridoo	Exercise of palate muscles	(34)
Oropharyngeal exercises (fixed set of exercises)	Exercise of muscles of oral cavity, pharynx, and neck	(35, 36)
Inspiratory muscle strength training	Exercise of muscles of inspiration	(37)
Expiratory muscle strength training	Exercise of muscles of expiration	(38)
Myofunctional therapy (exercises selected according to practitioner evaluation)	Exercise of muscles of oral cavity, pharynx, and neck	(41, 42)
Frenuloplasty	Release of ankyloglossia	None
Daytime electrical stimulation of the tongue	Increases muscle strength of the tongue	(43)
Nightlase	Tissue stiffening and potential shrinkage of soft-palate, tongue, and lateral pharyngeal tissues with Nd:YAG and Er:YAG laser	(48–50)
Maxillary skeletal expanders (bionator, advanced Lightwire functional, Crozat, Frankel, and Schwartz)	Nonsurgical intraoral orthotics to expand and/or protrude the maxilla and/or mandible	None
Anterior growth guidance appliance	Fixed orthodontic appliances focused on the maxilla and/or mandible	None
Daytime nighttime appliance	Removable orthodontic devices focused on the maxilla and/or mandible	(55–57)
Orthotropic appliances	Combination of fixed and removable appliances applied to the preteenager to develop better oral and facial anatomy	None

Definition of abbreviations: Er:YAG = erbium-doped yttrium aluminum garnet; Nd:YAG = neodymium yttrium aluminum garnet.
*Case reports are not included.

and unpublished clinical trial results presented on company websites.

Position Therapy Devices

Positional OSA has been variably defined but generally occurs when the AHI in the supine body position is at least twice as great as that in nonsupine body positions (11). Because positional OSA is common (12), a wide range of devices have been developed to encourage nonsupine body positions during sleep to reduce gravitational forces on the upper airway and abdominal loading of the diaphragm. Passive positional therapy includes devices that produce mechanical discomfort when an individual is in the supine body position (e.g., a T-shirt with pocket to hold tennis balls over the back) or waist belts or backpacks to encourage a nonsupine body position and can also include elevation of the head of the bed (13). Active positional therapy includes two novel devices that deliver low-intensity vibration to wearers when supine. On the basis of encouraging pilot data (14), the Sleep Position Trainer (NightBalance; NightBalance B.V.) was evaluated in a randomized trial against a mandibular repositioning appliance. Among study participants with mild to moderate positional OSA, the Sleep Position Trainer demonstrated improvement in mean AHI from 13.0 events/h to 7.0 events/h ($P < 0.001$) in 45 study participants at 3 months (15) and from 13.2 events/h to 7.1 events/h in 29 participants followed for 12 months (16), with both improvements similar to the mandibular repositioning appliance. A randomized crossover study compared this device to automatically adjusting continuous PAP (CPAP) in 110 study participants with supine-only OSA (overall AHI >15 events/h and nonsupine AHI < 10 events/h); CPAP had a lower treatment AHI (decrease from baseline 21.5 events/h to 3.7 events/h with automatically adjusting CPAP vs. 21.5 events/h to 7.3 events/h with the device; $P < 0.001$), but the device had greater adherence (345 min/night vs. 287 min/night; $P < 0.0001$) (17).

The Neck Position Therapy Device (Night Shift; Advanced Brain Monitoring) showed a decrease in mean AHI from 24.7 events/h to 7.5 events/h ($P < 0.001$) in 30 study participants with positional OSA (18). Another randomized crossover study compared this device with automatically adjusting CPAP in 40 study participants with supine-only OSA (overall AHI >10 events/h and nonsupine AHI

<10 events/h); the automatically adjusting CPAP had lower AHI (baseline 23.4 events/h to 13.0 events/h with the device vs. 23.4 events/h to 4.0 events/h with automatically adjusting CPAP; $P = 0.001$) and a greater decrease in Epworth Sleepiness Scale score (adjusted difference in score change, 2.28; 95% confidence interval, 0.96–3.61; $P = 0.001$) and was also preferred by a majority of participants (60% vs. 20%) (19). Clinical and patient-reported outcomes have not been extensively investigated for these products. Despite these limitations, we recommend positional therapy as a treatment option for selected patients with clear evidence of supine-dependent OSA, particularly if positional therapy appears to resolve OSA on sleep testing and if PAP is not well tolerated. Positional therapy may also play an important role as adjunctive therapy or cotherapy after an incomplete response to surgery or mandibular repositioning appliances.

Nasal Treatments

Treatment of nasal obstruction has been shown not to improve the AHI meaningfully, although there can be improvement in other measures of sleep-disordered breathing or symptoms (20). Nasal valve dilation and/or stabilization can be achieved with internal or external nasal dilators or with surgical devices or procedures, but there are no studies of OSA with isolated nasal valve dilation and/or stabilization. There is one study of chin straps in adults with OSA that showed no improvement in AHI or other objective measures of sleep-disordered breathing (21). There are no published studies evaluating the use of breathing techniques (e.g., Buteyko), tapes, or other methods that forcibly close lips during sleep to prevent or minimize mouth breathing and encourage nasal breathing in adult OSA. Addressing nasal patency in patients with OSA is generally recommended because nasal obstruction can contribute to sleep-disordered breathing and sleep disturbances (22), be associated with decreased PAP adherence (23), or complicate mandibular repositioning appliance therapy (24).

Nasal expiratory PAP therapy (Provent Therapy; Provent Sleep Therapy, LLC) functions by providing very low inspiratory resistance to airflow but high expiratory resistance, thereby elevating end-expiratory PAP and helping maintain airway patency. After initial studies with devices of varying designs (25–27), additional studies were performed with a device having an expiratory resistance of 80 cm of water/L/s at a flow rate of 100 ml/s. A company-sponsored, multicenter randomized sham-controlled trial showed an improvement in the mean AHI from 14.4 events/h to 5.6 events/h ($P < 0.001$) in 127 study participants at 3 months that was greater than that in the sham control group (28). Forty-one study participants with good adherence and efficacy were then followed for 12 months, demonstrating consistent benefits over time (29). However, another randomized trial not supported by the company showed no difference with active versus placebo device for change in AHI or daytime sleepiness (30). Furthermore, the devices used in these studies were poorly tolerated in clinical practice, potentially explaining the manufacturer's decision to decrease the expiratory resistance of current commercially available devices (<16 cm of water/L/s at a flow rate of 100 ml/s, per company personnel). A crossover study of 22 adults with OSA who did not achieve resolution of OSA with mandibular repositioning appliances showed that some patients experienced improved results with a custom-made oral expiratory PAP device (Oventus Medical Ltd.), with a greater benefit when the nasal expiratory PAP therapy device above was added (31). Our clinical experience with expiratory resistance has been generally disappointing, and thus we do not currently recommend this intervention.

Negative Pressure Therapy Devices

At least two approaches have used negative pressure. Oral pressure therapy (Winx; ApniCure) relied on negative intraoral pressure delivered with the use of a mouthpiece resting against the soft palate. In a multicenter, randomized trial of 63 participants with active treatment, this approach showed an improvement in the AHI from 27.5 to 13.4 events/h ($P < 0.001$) after 4 weeks of treatment (32). Continuous negative external pressure (cNEP; Sommetrics, Inc.) applies negative pressure to the neck skin through a soft cervical collar. In an open-label study of 15 participants, this therapy reduced the AHI from 43.9 to 11.2 events/h ($P < 0.001$) (33). Neither of these therapies is commercially available, and independent trials will be needed to assess outcomes and adherence.

Treatments Aimed at Increasing Muscle or Tissue Tone

Although many patients with OSA have upper airway anatomical compromise, a key component of OSA pathophysiology is the decrease in muscle tone during sleep. Numerous approaches have targeted upper airway muscles. An early study examining the potential role of muscle strengthening involved 25 adults, in whom didgeridoo playing almost daily for 4 months was associated with a decrease in the AHI from 22.3 to 11.6 events/h, a change greater than that in the control group (observation) (34). Building on this work, a Brazilian team conducted a randomized placebo-controlled trial of a specific set of 13 "soft palate, tongue, facial muscle, and stomatognathic function exercises" performed daily for 3 months, showing a decrease in the AHI from 22.4 events/h to 13.7 events/h ($P < 0.001$) among 16 study participants in the therapy group (35). A case series study from a journal not indexed in PubMed adopted a similar exercise program and showed an improvement in AHI (from 22.3 events/h to 11.5 events/h; $P < 0.001$) among 30 participants with mild to moderate OSA (36). A randomized controlled trial with 12 participants undergoing inspiratory muscle strength training (inspiration against resistance) showed no change in the AHI (21.9 events/h –26.4 events/h; $P = 0.29$; similar to the control group) (37). Another randomized controlled trial of expiratory muscle strength training (expiration against resistance) in 13 study participants found a 40% decrease in AHI (from approximately 16.5 events/h to 10.1 events/h) in the AHI after 5 weeks (38). The role of a specific exercise program has not been further examined in larger studies to support broad adoption.

Oral myofunctional therapy includes exercises drawn from speech language pathology to address speech and swallowing disorders and oral growth and development that are believed to be related to poor function or coordination of the muscles of the tongue, throat, and face. Oral myofunctional therapy involves the selection from among a number of exercises based on the assessment of a speech language pathologist, and published studies have not outlined a specific uniform exercise protocol for OSA or a protocol that could guide exercise selection. This key distinction

makes the above studies of defined exercise-based therapies (34–38) not applicable to oral myofunctional therapy because the latter includes different exercises for different individuals, a fact overlooked by previous systematic review authors (39, 40). The first randomized trial of oral myofunctional therapy alone in adults with OSA included 27 participants and showed an improvement in the AHI from 28.0 events/h to 13.9 events/h ($P < 0.001$), with no change in the control group (41). A second randomized controlled trial included 19 participants with mild to moderate OSA undergoing oral myofunctional therapy and showed no change in AHI (42). In both studies, there was no clear specification of how exercises were selected by practitioners, limiting the applicability of these findings. Frenuloplasty has been advocated as an adjunct procedure with oral myofunctional therapy, but there is no objective evidence to support the performance of frenuloplasty in adults with OSA.

Daytime electrical stimulation of the tongue has been developed and marketed as a treatment for snoring and mild OSA in the European Union, the United Kingdom, Canada, and Australia as Snoozeal (Signifier Medical Technologies). A recent case series study of 13 adults showed subjective improvements in snoring, but there were no data for posttreatment AHI (43). A previous study showed improvement in snoring but not in OSA (44). The publication of studies demonstrating clinical benefits in adults with OSA is required before this approach can be recommended widely as an alternative OSA treatment.

Carbon dioxide LASERs have been used to treat the soft palate (45, 46), but they have fallen out of favor because of their morbidity and lack of clear benefit in OSA (47). The erbium-doped yttrium aluminum garnet LASER has become popular in dental applications and LASER skin resurfacing on the basis of the potential for tissue stiffening because of changes in collagen subtypes after treatment (particularly collagen types I and III). More recently, neodymium yttrium aluminum garnet and erbium-doped yttrium aluminum garnet LASERs have been combined and used in nonablative mode, which is marketed by the manufacturer as Nightlase (Fidelis and Lightwalker). Three case series studies have all shown no significant change in AHI (48–50). Without peer-reviewed published studies validating successful outcomes treating OSA with this LASER, we do not recommend this therapy.

Dental Procedures and Devices

Maxillofacial skeletal abnormalities are an important risk factor for OSA, especially in syndromic children or adults with retrognathia or underdeveloped dental arches. Improvement in maxillofacial structure can be achieved through a variety of methods that may affect airway dimensions and physiology. Mandibular repositioning appliances and tongue-retaining devices have demonstrated benefits in treating adult OSA (7, 8). Maxillomandibular surgical skeletal advancement (or bimaxillary advancement) offers consistent benefits based on a similar mechanism of action with the advantage of the advancement of the maxilla in addition to the advancement of the mandible without the requirement for the ongoing behavioral component of using a mandibular repositioning appliance during sleep (51).

Multiple orthodontic approaches have been used and examined in children, such as maxillary advancement or expansion, in whom there is some evidence of benefit, especially if combined with tonsillectomy and/or adenoidectomy in children without obesity (52). More recently, orthodontic approaches based on similar concepts have been proposed as adult OSA treatments. However, the concept of devices to expand dental arches or produce skeletal protrusion in adults is not supported by strong data or in systematic reviews from the orthodontic community (53). These airway-focused orthodontic approaches have scant scientific evidence and are presented in case series and case reports often confounded by the performance of other procedures (54). In addition to scientific evaluation, these airway-focused orthodontic approaches would need to be compared against traditional orthodontics to align teeth without additional skeletal expansion or protrusion to validate the hypothesis that specific expansion and/or protrusion through adult orthodontics positively impacts airway size or breathing during sleep. The research with these approaches has largely focused on changes in dental dimensions and maxillofacial bone growth without objective OSA outcomes.

Skeletal Expanders, including the Daytime Nighttime Appliance (BioModeling Solutions, Inc.), Advanced Lightwire Functional Appliance, and others, use nonsurgical intraoral orthotics in an attempt to expand and/or protrude the maxilla and/or mandible. Orthotropic appliances aimed toward guiding the growth of the facial bones may also include fixed orthodontic appliances to create space for the teeth and tongue to correct a patient's oral and head posture. Orthotropic approaches are specifically for preteenagers and are not applicable to adults. In general, these removable orthodontic devices lack rigorous clinical studies in adults to validate their effectiveness and to determine which OSA or skeletal morphometric subtypes might respond. One approach using the Daytime Nighttime Appliances has shown an approximately 50–60% improvement in the AHI in adults with OSA in three small case series studies (total $n = 43$) from online-only journals not indexed in PubMed (55–57). This limited scientific evaluation may be problematic when there are widespread programs marketed to train and encourage general dentists, who most often lack American Dental Association–accredited training, to use these removable appliances to "cure" OSA.

Moving Forward

We have seen many patients stop or delay effective therapy based on false hopes offered by unproven therapies. Thus, we believe strongly that responsible providers and others should educate their patients regarding proven therapies. Moreover, we call on regulatory authorities and advocacy efforts to do a better job controlling unproven or potentially harmful therapies.

We recognize that many other products are being aggressively marketed to patients with OSA without supportive data. PAP equipment-cleaning devices are being strongly recommended to patients with the threat that recurrent infections will otherwise result. This situation is occurring despite a recent U.S. Food and Drug Administration warning that these devices are not legally approved for marketing as devices to clean, disinfect, or sanitize PAP devices or accessories (masks, tubing, or headgear) and that there is potential harm (58). We have seen patients whose respiratory symptoms improve after stopping use of these unproven cleaning devices. We emphasize that regular soap

and water is sufficient to keep PAP devices clean. Moreover, there is no evidence of increased infection rates from PAP use. In addition, various pillows and pillow inserts are being marketed to treat OSA (in addition to restless legs, cerebral palsy, and other conditions) with no published data to our knowledge.

Pharmacotherapy for OSA has been a longstanding ambition for the field, as summarized in a recent systematic review (59). Despite recent advances, these therapies remain experimental, and we recommend robust clinical trials focused on patient-reported outcomes or objective clinical outcomes before such approaches can be generally endorsed.

There is a growing recognition that OSA is a highly heterogeneous disorder, with a variety of risk factors, clinical and physiological expressions of disease, and therapy responses. Precision medicine principles may allow the tailoring of therapy according to phenotypic and endotypic features at the individual patient level. It is incumbent on promoters of new therapies to evaluate which patients are best suited to them.

Conclusions

Adult OSA is common and associated with serious medical consequences. Healthcare providers should treat adults with OSA with evidence-based treatments that have peer-reviewed studies showing benefits or as part of investigational protocols, preferably rigorous clinical trials registered at ClinicalTrials.gov or a similar centralized database. PAP, upper airway surgery, mandibular repositioning appliances, hypoglossal nerve stimulation, and major weight loss have numerous such studies, providing a basis to define which treatments might be best for individual patients. The development of emerging OSA treatments is exciting, but currently many novel therapies marketed for supposedly benign snoring are then applied to OSA without supportive data. Practitioners must not be swayed by marketing claims advanced by manufacturers or other entities and must demand rigorous evaluation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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