Evidence Brief: Oral Appliances for Sleep-Related Breathing Disorders

Key Points

- The evidence reviewed in this brief consists of a 2015 clinical practice guideline from the American Academy of Sleep Medicine/American Academy of Dental Sleep Medicine (AASM/AADSM, based on a systematic review and meta-analysis), as well as a 2015 consensus guideline co-authored by dental sleep medicine societies in Italy; 6 randomized trials of oral appliances (OAs) published since the last literature search date of the 2015 AASM/AADSM guideline and that were not already included in the guideline; a 2015 review of systematic reviews; and 8 systematic reviews/meta-analyses published in 2015/2016, two of which were focused on pediatric populations.

- The evidence shows that oral appliances, specifically custom-made, titratable devices, can improve obstructive sleep apnea (OSA) in adult patients compared to no therapy or placebo devices.

- OAs are generally less effective than continuous positive airway pressure (CPAP), but have a role in patients who are intolerant of or who reject CPAP.

- The AASM/AADSM guideline/systematic review found that patient adherence with OAs was better than that for CPAP and that OAs have fewer adverse effects that result in discontinuation of therapy, compared with CPAP.

- The two recent systematic reviews evaluating the data for oral appliances in pediatric OSA found very limited published evidence for their use and called for additional short- and long-term evidence, especially for health outcomes, such as neurocognitive and cardiovascular function.

- Another gap identified is the lack of published comparative evidence evaluating comprehensive management of oral appliance therapy for OSA (i.e., diagnosis, treatment, and monitoring/titrating therapy) in dental versus other contexts.

Objective

The objective of this brief narrative review is to provide a summary of recent literature published in 2015 and 2016, including systematic reviews (SR), meta-analyses (MA), and selected randomized trials, for the use of oral appliances (e.g., mandibular advancement devices) in the management of sleep-related breathing disorders, principally obstructive sleep apnea/hypopnea syndrome (OSAHS or OSA). In addition, this brief will review and grade the clinical practice guidelines (CPGs) published in 2015: a SR/MA/CPG from the American Academy of Sleep Medicine (AASM) and the American Academy of Dental Sleep Medicine (AADSM) on the

treatment of obstructive sleep apnea and snoring with oral appliances[1] and a consensus guideline co-authored and published in 2015 from dental sleep medicine societies in Italy.[2]

This evidence brief was developed in response to ADA Resolution 96H-2015 – Development of ADA Policy on Dentistry's Role in Sleep-Related Breathing Disorders, which directed the Council on Scientific Affairs (CSA) to collaborate with other appropriate ADA agencies to develop policy on "dentistry's role in sleep-related breathing disorders." This brief narrative review is intended to provide a "state of the science" for oral appliances in the management of sleep-related breathing disorders, and will be shared with other ADA Councils (e.g., Council on Dental Practice) to inform discussion regarding the development of policy, as directed by the Resolution. This document was reviewed by a CSA-assembled workgroup (Appendix Table 1) of identified subject-matter experts, as well as members of the ADA Council on Dental Practice.

Background: Sleep-Related Breathing Disorders

Description. Sleep-related breathing disorders comprise a variety of diagnoses, including simple snoring, upper airway resistance syndrome (UARS), central sleep apnea/hypopnea syndrome (CSAHS), and obstructive sleep apnea/hypopnea syndrome (OSAHS or OSA).[3,4] Both snoring and OSA are common sleep disorders resulting from repetitive narrowing and collapsing of the upper airway.5 In the U.S. the prevalence of OSA is estimated to be 3% to 7% in men and 2% to 5% in women.6 Prevalence is higher, i.e., greater than 50%, in patients with cardiac or metabolic disorders, relative to the general population.[7]

Risk factors for OSA include obesity (the strongest risk factor), upper airway abnormalities, male sex, menopause, and age.[7] Untreated OSA is associated with multiple adverse sequelae, including systemic hypertension, coronary artery disease, stroke, atrial fibrillation, increased motor vehicle accidents, congestive heart failure, daytime sleepiness, decreased quality of life, and increased mortality.[7, 8] Snoring is also a significant social problem and contributes to decreased quality of life for bed partners through disrupted sleep and may have an independent negative effect on health (e.g., increased risk for cardiovascular disease or Type II diabetes mellitus).[9-11]

Diagnosis. Apneas are defined as temporary cessation of breathing of 10 seconds or more, while hypopneas are periods of shallow breathing that result in oxygen desaturation.[7] OSA is defined by the presence or absence of symptoms (e.g., daytime sleepiness, fatigue, snoring, choking during sleep, nocturia, alterations in performance) and objective assessment of the respiratory disturbance index (RDI; the number of apneas, hypopneas, and arousals from sleep because of respiratory efforts per hour of sleep).[7] OSA is the presence of subjective symptoms plus an RDI of 5/hr or greater or an RDI of 15/hr in the absence of symptoms.[7] OSA severity is classified by the number of apneas and/or hypopneas per hour of sleep as detected by polysomnography, known as the Apnea/Hypopnea Index (AHI); an AHI of 5 to 15/hr is considered mild, 16 to 30 moderate, and greater than 30/hr severe OSA). Another measure of OSA severity is the oxygen desaturation index (ODI).[12] The ODI, which is also evaluated during sleep studies, measures the number of times per hour of sleep that the blood's oxygen level drops by a certain percentage from baseline.[12]

The standard for diagnosis of OSA is overnight, attended polysomnography to detect the frequency of apneic and hypopneic events, traditionally done as a standardized, facility-based technique, with multichannel recordings that determine sleep time, sleep stages, respiratory effort, airflow, cardiac rhythm, oximetry, and limb movements.[4, 5] However, there are portable sleep monitors that may be used in-home; these monitors include at least 3 sensors that detect respiratory events in the home setting.[5] The AASM recommends considering these in patients with a high pretest likelihood for moderate-to-severe OSA without other substantial comorbid conditions.[5, 13] A 2014 clinical practice guideline14 from the American College of Physicians (ACP) provided the following recommendations regarding sleep studies in the diagnosis of OSA in adults:

Recommendation 1: ACP recommends a sleep study for patients with unexplained daytime sleepiness. (Grade: weak recommendation, low-quality evidence)

Recommendation 2: ACP recommends polysomnography for diagnostic testing in patients suspected of obstructive sleep apnea. ACP recommends portable sleep monitors in patients without serious comorbidities as an alternative to polysomnography when polysomnography is not available for diagnostic testing (Grade: weak recommendation, moderate-quality evidence)

Excessive daytime sleepiness, which is the most common daytime symptom, is measured by the Epworth Sleepiness Scale (ESS), which is a subjective, a self-administered questionnaire measuring the patient's assessment of how likely they are to nod off doing usual daily activities (e.g., watching television).[15] Other questionnaires such as the STOP-BANG[16, 17] or Berlin questionnaire[18] evaluate both daytime alertness and sleep variables (e.g., snoring, breathing problems during sleep), as well as presence of risk factors such as high BMI and hypertension. The Sleep Apnea Quality of Life Scale is a validated instrument for evaluating disease-related quality of quality of life.[19]

Treatment. First-line therapy, especially for severe OSA, is use of continuous positive airway pressure (CPAP) devices during sleep.[5, 20, 21] CPAP uses pressure to counteract airway narrowing through the delivery of compressed air to the oropharynx, thereby splinting the airway (i.e., keeping it open with increased air pressure) and maintaining airway patency.[5, 20] CPAP devices are available with a wide variety of mask types and machine sizes.[5] When used properly and consistently, CPAP can result in improved sleep patterns and quality of life.[20] However, these devices may not be well tolerated by patients and adherence to therapy may be an issue.[5, 20] Data on adherence to CPAP, defined as 4 hours or more of use per night, are reported to range from 17% to 60%.[22, 23] CPAP therapy also may not fully resolve the OSA.[20]

Another commonly used treatment is oral appliance (OA) therapy. OAs can be divided into three general groups: soft-palate lifters (which are virtually no longer in use), tongue-retaining devices, and mandibular advancement appliances (MAA).[24] Tongue-retaining devices are rarely used, mainly if there are dental reasons precluding the use/construction of MAA.[24] The most commonly used type of OA is a mandibular advancement device that either advances the mandible over time (i.e., adjustable) or provides a fixed protrusion of the mandible.[24] Mandibular advancement moves the tongue base forward, and enlarges the retropharyngeal region.[5, 24] The

most frequent adverse effects of these devices include excessive salivation, mouth and teeth discomfort, temporomandibular adverse effects, and orthodontic changes.[24, 25] Summary compliance data from 2007 showed that at 30 months, 56% to 68% of patients continue to use an oral appliance.[24]

There are also surgical treatments, which are used less commonly; these include removal of tissue from the posterior pharyngeal region (e.g., laser-assisted uvulopalatoplasty [LAUP]) and maxillary-mandibular advancement, in which both the maxilla and the mandible are surgically advanced, thereby permanently enlarging the posterior pharyngeal region.[5] Other interventions include devices to alter sleep position, physical therapy to improve oropharyngeal muscle tone, atrial overdrive pacing for patients with nocturnal bradycardia, complementary and alternative medicine, interventions to achieve weight loss, including bariatric surgery, and avoidance of alcohol and tobacco.[20, 26]

Dental Specialty Society Statements. A statement[27] from the Canadian Dental Association (CDA; approved by the CDA Board of Directors in 2005 and revised November 2012) recommends that before a dentist prescribes an oral appliance for snoring indications, the patient be referred for a medical assessment to determine the presence and severity of OSA. Further, the medical assessment should "provide confirmation that snoring may be treated independently, or, if obstructive sleep apnea is involved, in cooperation with an attending physician."

A 2013 position paper overview from the American Association of Oral and Maxillofacial Surgeons (AAOMS)[28] on "Evaluation and Management of Sleep Apnea" states, as follows:

"Oral appliances have been shown to be an effective therapy in a significant percentage of patients with mild to moderate OSA. While not considered a first-line treatment in patients with OSA, custom-made oral appliances may be indicated for use in patients with severe OSA who have failed first-line treatment with CPAP. Oral appliances should be fitted by qualified dental personnel who are trained and experienced in the overall care of oral health, the temporomandibular joint, dental occlusion and associated dental structures …"

The AAOMS position paper overview also states that although oral and maxillofacial surgeons are "uniquely qualified to provide diagnostic input … into the evaluation of patients suspected of having OSA … [u]sing all available data, the diagnosis of OSA is ultimately made by a qualified physician who is trained in sleep medicine."

Methods

MEDLINE® was searched (via PubMed) 12/11/15 with the terms "((mandibular advancement) OR (oral appliance*)) AND sleep," resulting in 1269 hits. The search was downloaded into an EndNote® database and titles and abstracts were reviewed to identify relevant clinical practice guidelines, systematic reviews, technology assessments, and meta-analyses published in 2015, as well as randomized trials published since the last search date of the 2015 AASM/AADSM systematic review/clinical practice guideline[1] (February 2013) not already included in the

guideline. Bibliographies of selected articles were further examined for relevant references. This search was updated 04/18/16.

Evidence Review

Clinical Practice Guidelines

Ramar et al. 20151: In 2015, the AASM/AADSM published a systematic review/meta-analysis/clinical practice guideline1 on the treatment of obstructive sleep apnea and snoring in adults with oral appliance therapy. The primary objective of the 2015 document was to update the prior 2006 AASM guideline and systematic review.[29, 30] Eleven PICO (Patients, Interventions, Comparisons, Outcomes) questions were developed (see Appendix Table 2) and were used to formulate the literature search strategies. Searches of the MEDLINE (via PubMed) and EMBASE databases were first performed in July and August 2012, respectively, and subsequently updated in February 2013.

Search results were limited to: humans, English, all adults (no pediatrics), and RCTs (although the RCT restriction was not used for PICO questions 7 and 11, owing to a lack of trials available). Articles were excluded if they focused on diagnosis, described the use of OAs to treat central or complex sleep apnea, or if they evaluated treatment in pediatric patients. A total of 51 articles met the inclusion criteria and were used for data extraction, meta-analysis, and quality grading.

Evidence quality was assessed according to a modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. Meta-analysis was performed with Review Manager 5.2 and all analyses were performed using a random-effects model. The AASM/AADSM Task Force then developed strengths of recommendation based on both the strength of evidence and an assessment of the relative benefits of the treatment versus the potential risks (see Appendix Table 3). The strength of each recommendation also incorporated patient preference along with other factors such as cost, value, and other patient-related factors.

The authors acknowledged that for the treatment of OSA, the evidence available for analysis of oral appliances was limited. Meta-analysis showed that oral appliances can reduce arousal index, AHI, and oxygen desaturation index, and increase oxygen saturation index; however, CPAP was more effective than oral appliances on each of these parameters.

Other meta-analytic findings:

- Oral appliances have no significant effect on sleep architecture (i.e., % REM sleep) or sleep efficiency (i.e., % of time spent in bed asleep).
- Oral appliances improve quality of life measures and decrease excessive daytime sleepiness in adult patients with OSA and are nearly equivalent or equivalent to CPAP on both of these, respectively.

- OAs are modestly effective in reducing blood pressure and are nearly equivalent to CPAP for this outcome.
- Patient adherence with oral appliances is better overall than with CPAP in adult patients with OSA and serious adverse effects resulting in discontinuation of oral appliance therapy are less common than serious adverse effects causing discontinuation of CPAP.

The summary of AASM/AADSM recommendation statements appears in Table 1.

Table 1. AASM/AADSM Summary of 2015 Recommendation Statements

Recommendation Statement	Strength of Recommendation[a]	Quality of Evidence	Benefits vs. Harms/Burdens Assessment
The Use of Oral Appliances for Treatment of Primary Snoring in Adults			
We recommend that sleep physicians prescribe oral appliances, rather than no therapy, for adult patients who request treatment of primary snoring (without obstructive sleep apnea).	Standard	High	Benefits clearly outweigh harms
The Use of Oral Appliances for Treatment of Obstructive Sleep Apnea in Adults			
When oral appliance therapy is prescribed by a sleep physician for an adult patient with obstructive sleep apnea, we suggest that a qualified dentist use a custom, titratable appliance over non-custom oral devices.	Guideline	Low	Benefits clearly outweigh harms
We recommend that sleep physicians consider prescription of oral appliances, rather than no treatment, for adult patients with obstructive sleep apnea who are intolerant of CPAP therapy or prefer alternate therapy.	Standard	Moderate	Benefits clearly outweigh harms
We suggest that qualified dentists provide oversight — rather than no follow-up — of oral appliance therapy in adult patients with obstructive sleep apnea, to survey for dental-related side effects or occlusal changes and reduce their incidence.	Guideline	Low	Benefits clearly outweigh harms
We suggest that sleep physicians conduct follow-up sleep testing to improve or confirm treatment efficacy, rather than conduct follow-up without sleep testing, for patients fitted with oral appliances.	Guideline	Low	Benefits **clearly** outweigh harms
We suggest that sleep physicians and qualified dentists instruct adult patients treated with oral appliances for obstructive sleep apnea to return for periodic office visits—as opposed to no follow-up—with a qualified dentist and a sleep physician.	Guideline	Low	Benefits clearly outweigh harms

[a]See Appendix Table 3

The AASM/AADSM guideline provides a section outlining research gaps and suggestions for future research, including:

- adoption of a consistent and standardized nomenclature when referring to oral appliances;
- obtaining objective, rather than subjective, assessments of treatment adherence to oral appliance therapy;
- development of a consistent and objective measure of snoring to evaluate benefit of oral appliance therapy;
- standard protocols to document adverse effects related to oral appliances;
- larger and longer RCTs examining the benefits of oral appliance therapy on cardiac, metabolic, and neurocognitive health as well as studies evaluating long-term outcomes associated with oral appliance therapy in adult patients with OSA; and
- future studies to evaluate cost-benefit analysis and effectiveness compared to CPAP.

Definitions. The AASM/AADSM guideline uses the term "qualified dentist" as "the dental provider of choice to provide oral appliance therapy." Although not explicitly supported by an evidence base, the guideline developers assert that "successful delivery of oral appliances requires technical skill, acquired knowledge, and judgment regarding outcomes and risks of these therapies" and that "The need to append the word 'qualified' stems from two things: (1) all of the studies conducted to evaluate the efficacy and risks of oral appliances were conducted by dentists with considerable experience in dental sleep medicine, and (2) the unfortunate fact that training in dental sleep medicine is uncommon." Also, "[f]or the purposes of this guideline, a sleep physician is defined as a physician who is either sleep board-certified or sleep board-eligible." The AADSM published a definition of an "effective" OA in 2014, focusing on custom-titratable OAs. This definition was developed via consensus of a group of experienced dental sleep medicine researchers and clinicians using a modified RAND Appropriateness Method.[31]

AGREE-II Group Guideline Appraisal. In January 2016, three staff members of the ADA Scientific Information department undertook a group appraisal of the AASM/AADSM guideline using the Appraisal of Guidelines for Research & Evaluation-II (AGREE-II) instrument tool.[32] The AGREE-II rates each of 23 key items across 6 domains (i.e., Scope and Purpose; Stakeholder Involvement; Rigor of Development; Clarity of Presentation; Applicability; and Editorial Independence), followed by two global rating items (i.e., "Overall Assessment). The 23 key items and the two global rating items are rated on a 7-point scale (1 – strongly disagree to 7 – strongly agree). The calculated group scores for the 6 main domains can be found in Table 2.

Table 2. AGREE-II Domain Scores for the ADA Group Appraisal of the AASM/AADSM Clinical Practice Guideline (Ramar et al. 2015)[1]

Domain (Description)	Group Appraisal Score
Domain 1. Scope and Purpose (the overall aim of the guideline, the specific health questions, and the target population [items 1-3])	89%
Domain 2. Stakeholder Involvement (the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users [items 4-6])	69%
Domain 3. Rigor of Development (the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them [items 7-14])	75%
Domain 4. Clarity of Presentation (the language, structure, and format of the guideline [items 15-17])	85%
Domain 5. Applicability (identification of the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline [items 18-21])	32%
Domain 6. Editorial Independence (the formulation of recommendations not being unduly biased with competing interests [items 22-23])	64%

The group score for the overall assessment of quality of the guideline was 72%; 2 of the raters indicated they would recommend the guideline, while one indicated recommendation of the guideline with reservations." The AGREE-II User's Manual states that "although the domain scores are useful for comparing guidelines and will inform whether a guideline should be recommended for use, the Consortium has not set minimum domain scores or patterns of scores across domains to differentiate between high quality and poor quality guidelines."

Levrini et al. 2015[2]: In 2015, a group of seven specialty societies in fields relevant to dental sleep medicine in Italy co-authored and published a consensus guideline on the "dental support in the treatment of obstructive sleep apnea syndrome." The primary objective of the document was "to present a set of proposed clinical recommendations aimed at Italian dentists involved in the management of patients with obstructive sleep apnea syndrome or snoring." Although no formal search strategy or literature base was delineated, the document seemed to be developed on the basis of an iterative consensus process that was "based on the available literature data." Where data were found to be absent, "conclusions were reached on the basis of a combined evaluation of the clinical and practical evidence together with expert opinion."

Four questions were addressed:

- What approaches, anamnestic and clinical, might be helpful to dentists seeking to identify adult patients affected by OSAS or snoring?
- When can an intraoral device be applied in an adult patient with OSAS or snoring?
- What are the features of a device employed for the treatment of adult patients affected by OSAS or snoring?

- What therapeutic process should the dentist follow in the case of an adult patient affected by OSAS or snoring?

Although each conclusion was associated with a level of evidence and a power of recommendation, the process by which these aspects were graded was not explicit and appeared to be based heavily on consensus and expert opinion. The recommendations were, as follows:

Oral appliances can be used to treat: simple snoring, in patients who do not respond to, or do not appear to be suitable candidates for behavioral measures such as weight loss or positional therapy; mild or moderate OSAS, in patients who prefer OAs to [CPAP] or who are not suitable candidates for CPAP, because of its failure or failure of behavioral approaches like weight loss or positional therapy; severe OSAS, in patients who do not respond to or do not tolerate CPAP and in whom no indication for either maxillofacial or [ear, nose , and throat] surgery appears applicable.

The guidelines concluded, "The application of oral appliances is highly desirable in cases of simple snoring or mild to moderate OSAS, whereas considerable caution is warranted when treating severe OSAS. It is fundamental to ensure that the patient understands his problem and, at the same time, to present all the various treatment options."

AGREE-II Group Guideline Appraisal. In April 2016, three staff members of the ADA Scientific Information department undertook a group appraisal of the Italian consensus guideline using the AGREE-II instrument.[32] The calculated group scores for the 6 main domains can be found in Table 2.

Table 2. AGREE-II Domain Scores for the ADA Group Appraisal of the Italian Consensus Guideline (Levrini et al. 2015)[2]

Domain (Description)	Group Appraisal Score
Domain 1. Scope and Purpose (the overall aim of the guideline, the specific health questions, and the target population [items 1-3])	61%
Domain 2. Stakeholder Involvement (the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users [items 4-6])	41%
Domain 3. Rigor of Development (the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them [items 7-14])	12%
Domain 4. Clarity of Presentation (the language, structure, and format of the guideline [items 15-17])	44%
Domain 5. Applicability (identification of the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline [items 18-21])	17%
Domain 6. Editorial Independence (the formulation of recommendations not being unduly biased with competing interests [items 22-23])	25%

The group score for the overall assessment of quality of the guideline was 17%; all three of the raters indicated they would not recommend the guideline.

Recent Randomized Trials

The following section reviews the randomized trials of oral appliances published since the last literature search date of the 2015 AASM/AADSM guideline and that were not already included in the guideline (e.g., the OA vs. CPAP RCT by Phillips et al. 201333).

OA vs. CPAP

Glos et al. 2015[34]: This trial evaluated the effect of a mandibular advancement device (MAD; SomnoDent®) versus CPAP on cardiovascular parameters and autonomic activity in a 2-period crossover design in which 48 patients were either randomized to the sequence MAD/CPAP (12 weeks of MAD followed by 12 weeks of CPAP; n=24) or the sequence CPAP/MAD (3 months of CPAP followed by 3 months of MAD; n=24); 40 patients completed the study. At baseline and after each treatment period, patients were assessed by polysomnography, as well as by a daytime cardiac autonomic function test that measured heart rate variability, continuous blood pressure, and baroreceptor sensitivity under conditions of spontaneous breathing. Both CPAP and MAD therapy "substantially eliminated apneas and hypopneas," although CPAP had a greater effect. During daytime with all conditions of controlled breathing, 3-minute mean values of continuous diastolic blood pressure were significantly reduced by both MAD and CPAP. Selective increases in high-frequency heart rate variability were observed with MAD therapy. No changes were observed for baroreceptor sensitivity with either treatment. The authors concluded that both MAD and CPAP result in similar beneficial changes in cardiac autonomic function during daytime, especially in blood pressure, but that CPAP was more effective than MAD in eliminating respiratory events.

OA vs. Inactive Controls

Durán-Cantolla et al. 2015[35]: This small, randomized, placebo-device-controlled, double-blinded, crossover trial evaluated the safety and efficacy of a mandibular advancement device (KlearWay™) in adult patients with confirmed diagnosis of mild-to-moderate OSA (5 ≤ AHI < 30) by polysomnography and chronic snoring. The active treatment arm received mandibular advancement to a maximum tolerable distance or to a minimum of 65% of the maximum protrusion, while the placebo arm received a splint in centric occlusion that did not provide mandibular advancement. Of 42 patients randomized, 38 completed the study. Patients received active or placebo device for 4 weeks of adaptation and 12 weeks of therapy and then crossed over to the other arm. After each sequence of treatment, patients were assessed by questionnaires, conventional polysomnography, and objective home measurement of patient snoring. MAD decreased AHI from 15.3 (+/-10.2) to 11.9 (+/-15.5; p <0.01 compared with placebo devices), while AHI increased in placebo device patients. A 50% reduction in AHI was achieved in 46.2% of active treatment patients and in 18.4% of the patients treated with placebo devices (p<0.01). The subjective evaluation of chronic snoring was improved in the MAD phase; however, the objective evaluation of snoring did not show significant improvements. The authors

concluded that "MAD could be considered in the treatment of mild-to-moderate OSA and chronic [snoring]."

Marklund et al. 2015[36]: This 4-month, randomized, single-blinded, parallel trial compared the efficacy of an active, adjustable (via Herbst mechanism), custom-made oral appliance versus an intraoral placebo appliance (no advancement) in terms of improvement in daytime sleepiness and quality of life in patients with daytime sleepiness and snoring or mild-to-moderate obstructive sleep apnea (AHI < 30). Of 96 patients randomized, 91 completed the trial (n=45 active device; n=46 placebo device). The primary study outcomes were daytime sleepiness (assessed by questionnaire) and quality of life (assessed by SF-36); secondary outcomes included AHI and sleep quality (assessed by polysomnography), headaches, and adverse effects. The trial failed on its primary outcomes, showing no difference between active device and placebo device in terms of self-reported daytime sleepiness or quality of life. However, there were relative improvements in the objective secondary outcomes of AHI: the active device decreased AHI from 15.6 (+/-9.8) to 6.7 (+/-4.9; p<0.001 compared with placebo device); there were no differences between groups in sleep quality or headaches. Snoring (p<0.001) and restless legs symptoms (p<0.02) were significantly improved in the active device arm, compared with the placebo device.

Quinnell et al. 2014[37]: This randomized, controlled, crossover trial compared three types of nonadjustable oral mandibular advancement devices ("boil and bite," patient-molded semi-custom, and fully custom monobloc) to no treatment for mild-to-moderate OASHS (AHI 5 to <30/h). Of 90 adult patients randomized, 74 completed all 4 crossover phases of the trial. Patients were either newly diagnosed and not requiring or rejecting CPAP or patients who were CPAP intolerant. Device-based treatment was 6 weeks (2 weeks of acclimatization and 4 weeks' treatment); no treatment was 4 weeks. One week of washout followed active treatments and outcomes were obtained at baseline and at the end of each treatment period. The primary outcome was AHI scored by a polysomnographer blinded to treatment. Secondary outcomes included subjective sleepiness, quality of life, resource use, and cost. All devices significantly reduced AHI and sleepiness compared with no treatment. Compliance was lower for the "boil and bite" appliance, which was the least preferred treatment at the end of the trial. Although all devices were cost-effective compared with no treatment, the semi-custom device was the most cost-effective. The authors concluded that the nonadjustable devices can achieve clinically important improvements in mild-to-moderate OSAHS and are cost-effective. Of those tested, the semi-custom device was considered by the authors as an appropriate first choice.

OA vs. OA

Bishop et al. 2014[38]: This small, randomized, crossover trial was designed to compare two different designs of mandibular repositioning appliances (MRAs) for treatment of OSA. Twenty-four subjects who were recruited consecutively following a diagnosis of OSA by polysomnography underwent an initial home sleep study to establish a baseline RDI. They were then randomized to one of two MRAs that differed in advancement hardware and acrylic configurations, both in bulk and interocclusal contact. Eighteen patients completed the study. The primary outcome of the study was change in the RDI; secondary outcomes included quality

of life, subjective sleepiness, oxygen saturation, and subjective feedback regarding experience with the device. At the end of research participation, patients were asked to choose between the two devices for ongoing treatment and their choice was recorded. There were no statistically significant differences in treatment outcomes between the two devices. There was a statistically significant preference for a device design with minimal coverage of teeth and palate ($p \leq 0.05$). The authors concluded that device selection should favor titratable, unobtrusive designs with appropriate construction to promote acceptance and adherence to therapy.

Geoghegan et al. 2015[39]: This was a prospective, randomized, crossover trial of treatment with two different mandibular advancement devices. Twenty-two subjects were randomly allocated to the monobloc/twin bloc treatment sequence and 23 subjects to the twin bloc/monobloc treatment sequence; of the 45 original subjects, 38 completed the trial. Lateral cephalograms were taken, and the Epworth Sleepiness Scale and the Sleep Apnea Quality of Life Index were completed at baseline. The treatment sequences consisted of a baseline evaluation, a 2-week acclimatization period and 10-week treatment phase, followed by full evaluation and a 2-week washout period. AHI was the primary outcome measure; secondary outcomes included subjective sleepiness and quality of life. Although both designs resulted in a significant change in AHI, the monobloc was significantly superior to the twin bloc. No differences were seen in the subjective indicators of sleepiness and quality of life. Significant but similar cephalometric changes were observed, indicating that both devices alter the position of the surrounding musculature and improve upper airway patency.

Other Systematic Reviews, Meta-Analyses, and "Reviews of Reviews" Published in 2015/2016

"Review of Reviews" by Johal et al. 2015[40]: A 2015 "review of reviews"[40] provided an overview and quality assessment of systematic reviews evaluating mandibular advancement splint therapy for OSA. The authors searched PubMed and relevant Cochrane Library databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects [DARE], and the Health Technology Assessment [HTA] database) in September 2013 to identify systematic reviews and assessed the quality of the reviews using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) validated tool (see Appendix Table 4 for AMSTAR criteria).

Eight systematic reviews,[30, 41-47] four incorporating meta-analyses, were identified that reported on objective and subjective outcome measures. The effectiveness of MAS therapy was compared to no treatment, non-active appliance, CPAP, surgical intervention, and a different MAS appliance. The quality of the reviews was reported as variable (median=7, range=3 to 11), with only two of higher quality (AMSTAR scores >10), one of them a Cochrane review.[44] The Cochrane review showed significant benefits of MAS therapy compared with inactive appliances in terms of both daytime sleepiness and AHI outcomes.

Johal et al. concluded that the results from the higher-quality systematic reviews of MAS therapy for OSA showed that oral appliances can improve OSA and recommended that, "Current reporting guidelines for systematic reviews (e.g., PRISMA) and sources of high-quality

existing reviews should be closely followed to enhance the validity and relevance of future reviews."

Table 3 provides an array of the systematic reviews and meta-analyses published in 2015 and 2016. The detail included in the table indicates whether meta-analysis was performed; what was the stated objective of the review; search sources (including gray literature), dates, and parameters of the literature search; whether included studies were restricted to English language only; the PICO (patients, interventions, comparators, and outcomes) question being addressed; whether the authors performed any risk of bias/quality analysis of the individual included studies or body of evidence considered in the review and what the findings of these analyses were; and what were the main conclusions of the review.

Table 3. Systematic Reviews and Meta-Analyses Published in 2015/2016 on Oral Appliance Therapy for SRBD

Review	MA	**Objective**	**Search Sources**	**Language Restriction**	**Study Designs (n)**	**PICO**	**RoB/Quality Rating(s) Used in Report: Findings**	**Conclusions**
Adult Populations								
Bartolucci et al.[48]	Y	To investigate the effectiveness of different mandibular advancement amounts in reducing AHI in adult pts with OSA	MEDLINE, Cochrane Database, Google Scholar Beta, ISI Web of Knowledge, Scopus, and LILACS 1/1/90 through 4/30/15; also gray literature and manual searches	N/A	RCTs (13)	In adult patients with OSA, what is the effectiveness of different mandibular advancement amounts in reducing AHI?	Cochrane Collaboration RoB tool (individual studies): Unclear/Low RoB for most of the included studies GRADE (body of evidence): Moderate	There is small body of moderate quality evidence to suggest that **increasing the mandibular advancement does not produce significant improvements in the success rate since there is a high inter-individual variability in response to the MAD therapy**.
Bratton et al.[49] (2015a)	Y	To compare using network meta-analysis the association of CPAP, MADs, and inactive control groups (placebo or no treatment) with changes in SBP and DBP in adult (>18y) pts with OSA	MEDLINE, EMBASE, and Cochrane searched from inception through 8/15; study bibliographies reviewed	English	RCTs (51)	In adult patients with OSA, are CPAP, MADs, or no treatment associated with an effect on SBP or DBP?	Cochrane Collaboration RoB tool: In most domains, the majority of trials were at low risk, except for the allocation concealment category in which most trials were at an unclear risk due to inadequate reporting of methods.	Among patients with obstructive sleep apnea, **both CPAP and MADs were associated with reductions in BP. Network meta-analysis did not identify a statistically significant difference between the BP outcomes associated with these therapies**.
Bratton et al.[50] (2015b)	Y	To compare using network meta-analysis and quantify the effects of CPAP and MADs on ESS and to establish predictors of response to CPAP in adult (>18y) pts with OSA	MEDLINE and the Cochrane Library from inception to 5/31/15 using the Cochrane Highly Sensitive Search Strategy	English	RCTs (67)	In adult patients with OSA, what is the effect of MADs compared with CPAP on daytime sleepiness?	Cochrane Collaboration RoB tool: "The risk of selection bias was unclear in most studies because they did not adequately describe their methods of randomisation and allocation concealment. Additionally, most studies were deemed to be at high risk of performance and detection bias because they compared treatments that could not be masked (eg, continuous positive airway pressure vs no treatment or mandibular advancement devices)."	**[CPAP] and [MADs] are effective treatments for reducing daytime sleepiness in patients with [OSA]. [CPAP] seemed to be a more effective treatment than [MADs]**, and had an increasingly larger effect in more severe or sleepier OSA patients when compared with inactive controls. **However, [MADs] are an effective alternative treatment should [CPAP] not be tolerated.**

Table 3. Systematic Reviews and Meta-Analyses Published in 2015/2016 on Oral Appliance Therapy for SRBD (cont'd)

Review	MA	Objective	Search Sources	Language Restriction	Study Designs (n)	PICO	RoB/Quality Rating(s) Used in Report: Findings	Conclusions
Adult Populations (cont'd)								
Sharples et al.[51]	Y	To update systematic reviews of the effects of MAD and CPAP, compared with each other and with conservative management, and to estimate the effect on AHI and ESS of both treatments in adult (>16y) pts with OSA	MEDLINE, Embase and the Science Citation Index searched from 6/08 through 8/13. Reference lists of papers were searched; the research team's experts were asked to identify other trials missed in updated searches	English	RCTs (71 trials, 77 separate comparisons)	In adult patients with OSAHS, what is the effect of MADs compared to CPAP or either to conservative management on AHI and sleepiness?	The Jadad score (0 [poor] to 5 [rigorous]) was calculated as a measure of quality for consistency with previously published reviews: the Jadad score was available for 69/71 trials, with average score "close to three" for comparisons against CM. The mean Jadad score "was 2.9 in MAD-CM trials, 2.3 in MAD-CPAP comparisons and 3.1 in CPAP-CM trials, with the lower mean scores in MAD-CPAP comparisons mainly attributable to the difficulty in blinding the two active treatments."	Both MAD and CPAP are clinically effective in the treatment of OSAHS. **Although CPAP has a greater treatment effect, MAD is an appropriate treatment for patients who are intolerant of CPAP and may be comparable to CPAP in mild disease.**
Serra-Torres et al.[26]	N	To assess the effectiveness of [MADs] in treating adults with OSAHS, based on polysomnographic measurements such as the AHI and oxygen saturation, and on changes in the upper airway and improvements in snoring and somnolence; adverse effects were also noted	MEDLINE, Scopus, and Cochrane Library databases were searched for studies published between 2004 and 2014	None	SRs and MAs, RCTs, cohort studies, and case-control studies, prospective and retrospective (22)	In adult patients with OSAHS, do MADs compared to placebo devices or no treatment have an effect on AHI, changes in the upper airway, sleepiness, or snoring, and what is the adverse effect profile of MADs?	Modified CONSORT: Of the 25 studies, 3 were excluded because they were considered to be of low quality. Of the remaining 22 articles, quality was considered to be high in 16 cases and medium in 6.	**Using [MADs] during the hours of sleep helps to prevent snoring and excessive daytime sleepiness, reduce the AHI significantly, and bring about beneficial changes in the upper airway. Adjustable and custom-made [MADs] give better results than fixed and prefabricated appliances.** Monobloc devices give rise to more adverse events, although these are generally mild and transient.

Table 3. Systematic Reviews and Meta-Analyses Published in 2015/2016 on Oral Appliance Therapy for SRBD (cont'd)

Review	MA	Objective	Search Sources	Language Restriction	Study Designs (n)	PICO	RoB/Quality Rating(s) Used in Report: Findings	Conclusions
Adult Populations (cont'd)								
Zhu et al.[52]	Y	To evaluate the effectiveness of oral appliances for managing adult patients with OSA.	PubMed, Web of Science, Embase, Cochrane Central Register of Controlled Trials, and SIGLE were searched from 1/80 to 9/15	None	RCTs and nonrandomized trials of oral appliances compared to placebo devices or untreated controls (17)	In adult patients with OSAS, do oral appliances compared to placebo devices or no treatment have an effect on AHI, respiratory arousal index, minimum oxygen saturation, rapid eye movement sleep, sleep efficiency and ESS?	Cochrane Collaboration RoB tool for individual studies: 13 were high RoB, 3 were medium RoB, and one was low RoB GRADE to assess the quality of each outcome evaluated: quality of evidence of outcomes in this MA was assessed to be low	**The available evidence indicates benefits in respiration and sleep quality with oral appliances as compared to placebo devices or blank control**, while we cannot determine its effectiveness in sleep efficiency and sleep architecture alterations. **However, due to low evidence quality as revealed by GRADE, this finding should be interpreted with caution.**
Pediatric Populations								
Huynh et al.[53]	Y	To investigate the efficacy of orthopedic mandibular advancement and/or rapid maxillary expansion in the treatment of pediatric (<18y) obstructive sleep apnea	MEDLINE (1946-4/14), and Embase (1974-4/14). Google and Google scholar were searched for eligible studies published until 4/14.	English	Treatment arms of RCTs and nonrandomized controlled designs and before-after studies (8)	In pediatric patients (<18y) with OSAS, do MADs or rapid maxillary expansion devices have an effect on AHI, oxygen saturation (%), arousal index, increase in upper airway volume, or sleep quality?	Modified criteria from ARRIVE guidelines for human experimental studies. An intraclass correlation coefficient evaluated agreement between reviewers. Although no quality assignments were reported, the intraclass correlation coefficient was reported to be 0.85, indicating "almost a perfect" agreement among the three reviewers concerning the designated articles.	Although the included studies were limited, these orthodontic treatments may be effective in managing pediatric snoring and obstructive sleep apnea. Other related health outcomes, such as neurocognitive and cardiovascular functions have not yet been systematically addressed.

Table 3. Systematic Reviews and Meta-Analyses Published in 2015/2016 on Oral Appliance Therapy for SRBD (cont'd)

Review	MA	Objective	Search Sources	Language Restriction	Study Designs (n)	PICO	RoB/Quality Rating(s) Used in Report: Findings	Conclusions
Pediatric Populations (cont'd)								
Nazarali et al.[54]	N	To evaluate the effectiveness of mandibular advancement appliances (MAAs) for treatment of pediatric (<16y) OSA.	PubMed, EMBASE, MEDLINE, Healthstar, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (inception to 8/14). Hand searches of relevant article reference lists and limited grey literature and Google Scholar searches	English	RCTs or nonrandomized clinical trials, prospective or retrospective (4)	In pediatric (<16y) patients with OSAS, does treatment with a MAA compared with control or before/after have an effect on AHI, oxygen desaturation, daytime/nocturnal symptoms, or dental/skeletal changes?	Cochrane RoB tool: All included studies were found to have high RoB potential. Common weaknesses identified were nonrandomized allocation and small sample sizes. Further, two studies did not include a non-treated control group A meta-analysis was not possible due to the heterogeneity in study designs and collected information. Therefore, assessment of the RoB across studies was not feasible (GRADE framework).	The current limited evidence may be suggestive that MAAs result in short-term improvements in AHI scores, but it is not possible to conclude that MAAs are effective to treat pediatric OSA. Medium- and long-term assessments are still required.

AHI: apnea–hypopnea index; ARRIVE: Animal Research: Reporting In Vivo Experiments; BP: blood pressure; CM: conservative management; CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; ESS: Epworth Sleepiness Scale; LILACS: Latin American and Caribbean Health Sciences; MA: meta-analysis; MAA: mandibular advancement appliance; MAD: mandibular advancement device; N: no; N/A: Not available; OSA: obstructive sleep apnea; OSAHS: obstructive sleep apnea hypopnea syndrome; PICO: patients; interventions, comparator, outcome; pt(s): patient(s); RCT(s): randomized, controlled trial(s); RoB: risk of bias; SBP: systolic blood pressure; SIGLE: System for Information on Grey Literature in Europe; SR: systematic review; SRBD: sleep-related breathing disorder; Y: yes; y: years

Summary/Discussion

The evidence reviewed in this brief consists of a 2015 clinical practice guideline from the American Academy of Sleep Medicine/American Academy of Dental Sleep Medicine (AASM/AADSM, based on a systematic review and meta-analysis),[1] as well as a 2015 consensus guideline co-authored by dental sleep medicine societies in Italy;[2] 6 randomized trials of oral appliances published since the last literature search date of the 2015 AASM/AADSM guideline and that were not already included in the guideline;[34-39] a 2015 review of systematic reviews;40 and 8 systematic reviews/meta-analyses published in 2015/2016,[26, 48-54] two of which were focused on pediatric populations.[53, 54]

The evidence shows that oral appliances, specifically custom-made, titratable devices, can improve OSA in adult patients compared to no therapy or placebo devices. OAs are generally less effective than CPAP, but have a role in patients who are intolerant of or refuse CPAP. The AASM/AADSM guideline found that patient adherence with OAs was better than that for CPAP and that OAs have fewer adverse effects that result in discontinuation of therapy, compared with CPAP.

Gaps

The two systematic reviews[53, 54] evaluating the data for oral appliances in pediatric OSA found very limited evidence for their use and called for additional short- and long-term evidence, especially for health outcomes, such as neurocognitive and cardiovascular function.

Another gap identified is the lack of published comparative evidence evaluating comprehensive management of oral appliance therapy for OSA (i.e., diagnosis, treatment, and monitoring/titrating therapy) in dental versus other contexts.

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Appendix

Appendix Table 1. ADA Council on Scientific Affairs (CSA) Oral Appliances Evidence Workgroup

Workgroup Member	Affiliation
Angelo J. Mariotti, D.D.S., Ph.D. Workgroup Chair Member, CSA	• Chair, Division of Periodontology and Professor • The Ohio State University College of Dentistry • Columbus, OH
Henry A. Gremillion, D.D.S., M.A.G.D.	• Dean, Louisiana State University School of Dentistry • E.E. Jeansonne Endowed Professor in Continuing Dental Education • New Orleans, LA
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Paul McLornan, D.D.S.	• Board-certified prosthodontist in private practice in San Antonio • Assistant professor at University of Texas San Antonio Dental School and on the graduate faculty of the UTHSCSA Graduate School of Biomedical Sciences • San Antonio, TX
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Harold Smith, D.D.S.	• Diplomate of the American Board of Dental Sleep Medicine • Clinical Director, Dental Sleep Medicine of Indiana • President-Elect of the American Academy of Dental Sleep Medicine • Indianapolis, IN

Appendix Table 2. PICO Questions Developed for the 2015 AASM/AADSM Guideline[1]

PICO Question 1	In adult patients with primary snoring, do oral appliances (OAs) improve snoring, sleep quality, including the bed partner's sleep quality, and/or quality of life measures compared to other therapies or no treatment?
PICO Question 2	In adult patients with obstructive sleep apnea (OSA) (irrespective of underlying severity of OSA, and for each mild, moderate, or severe OSA), do oral appliances improve the apnea hypopnea index (AHI)/respiratory disturbance index (RDI)/respiratory event index (REI), oxygen saturation, arousal index, and/or sleep architecture compared to other therapies or no treatment?
PICO Question 3	In adult patients with OSA, do OAs improve cardiovascular endpoints, such as hypertension, coronary artery disease, myocardial infarction, and/or arrhythmias, as compared to other therapies or no treatment?
PICO Question 4	In adult patients with OSA, do OAs improve quality of life measures, and/or objective and subjective daytime sleepiness, as compared to other therapies or no treatment?
PICO Question 5	In adult patients with OSA, do titratable OAs improve AHI/RDI/REI, oxygen saturation, arousal index, and/or sleep architecture and do they improve long-term management of OSA with outcome measures such as AHI/RDI/REI, sleep quality, quality of life measures, cardiovascular endpoints, and/or subjective/objective measures of sleepiness compared to non-titratable OAs?)
PICO Question 6	In adult patients with OSA, do OAs lead to mild or serious side effects compared to those treated with other therapies or no treatment?
PICO Question 7	In adult patients with OSA, do follow-up oximetries, home sleep apnea tests, polysomnograms, or follow-up with a sleep physician improve long-term management with OAs as compared to no follow-up?
PICO Question 8	In adult patients with OSA, does follow-up with dentists/sleep specialists improve adherence and reduce side effects associated with OAs compared to those who do not have follow-up?
PICO Question 9	In adult patients with OSA, does OA use show better adherence than that reported by subjective or objective measures for PAP therapy?
PICO Question 10	In adult patients with OSA, do different types of OAs have variable effectiveness in controlling sleep-disordered breathing as measured by the AHI/RDI/REI and/or other outcome measures such as sleep quality, quality of life measures, cardiovascular endpoints, and/or objective/subjective daytime sleepiness?
PICO Question 11	In adult patients with OSA, what are the factors that predict success with OAs compared to other therapies or no treatment?

Appendix Table 3. AASM Strengths of Recommendations[1]

Assessment of Benefits versus Harms/Burdens	Overall Quality of Evidence			
	High	Moderate	Low	Very Low
Benefits clearly outweigh harms/burdens	Standard	Standard	Guideline	Option
Benefits closely balanced with harms/burdens OR Uncertainty in the estimates of benefits versus harms/burdens	Guideline	Guideline	Option	Option
Harms/burdens clearly outweigh benefits	Standard	Standard	Standard	Standard

Appendix Table 4. AMSTAR Criteria[55] for Assessing Quality of Systematic Reviews

Provision of a priori design
Duplicate study selection and data extraction
Comprehensive literature search
Publication status used as inclusion criterion
Listing of included and excluded studies
Provision of characteristics of included studies
Assessment and documentation of scientific quality of included studies
Appropriate use of scientific quality of included studies to formulate conclusions
Appropriate methods used to combine findings
Assessment of publication bias
Stated conflict of interest