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Review Article

Review of systematic reviews on mandibular advancement oral appliance for obstructive sleep apnea: The importance of long-term follow-up

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SUMMARY

The purpose of this review was to present the currently available information on oral appliance (OA) therapy for dentists, especially clinic-based dentists, to aid them in performing this treatment for the management of symptoms of obstructive sleep apnea (OSA). The clinical research evidence comprised of systematic reviews concerned with the mandibular advancement oral appliance (OAm). Continuous positive airway pressure (CPAP) is superior to OA therapy in improving OSA symptoms. It is necessary to survey the adherence of patients who stopped CPAP therapy to OAm therapy. There is little evidence supporting the theory that OAm therapy prevents cardiovascular disease or improves prognosis. There is still room to investigate the types of OAm. OAm therapy has clear dental and skeletal side effects with long-term use, and these are important for dentists. However, a certain percentage of patients discontinue consultations. Regarding consultation rate for follow-up and repair/adjustments of OAm, there are advantages for the clinic-based dentists treating OSA with OAm. We believe that enhancing under-graduate and post-graduate education on sleep medicine, and establishing a specialist system could be the strategies for enabling the dentists to handle OAm therapy in dental clinics.

1. Introduction

Oral appliance (OA) therapy for obstructive sleep apnea (OSA) attracted attention in the Western countries in the early 1990s. In Japan, OA became an accepted treatment option for OSA in the mid-1990s, and was introduced into the National Health Insurance in 2004. OSA is normally diagnosed by doctors. This is because many sleep disorders exist as a differential diagnosis. When doctors select OA as the mode of treatment, they request the dentist to fabricate the device. If the patients report with a referral from a doctor, they are eligible to receive OA therapy through the National Health Insurance.

The dentists who collaborate with specialists in sleep medicine perform OA therapy. These are usually dentists working at general hospitals or dental hospitals. Dental students in Japan also have received sufficient education on OA therapy for OSA. Some textbooks on OA therapy for OSA have been published, and scientific organizations of sleep dental medicine have been inaugurated in many countries including Japan. There will now be more opportunities for clinic-based dentists to handle OA therapy. Hence, we reviewed the currently available evidence on OA therapy and provide the information useful for clinic-based dentists to perform OA therapy. In particular, we have focused on and discussed the importance of follow-up monitoring. Regarding the type of OA, mandibular advancement oral appliance (OAm) has been considered more mainstream. The clinical research evidence used systematic reviews (SR) on OAm for this study.

2. Review of SRs

2.1. Search results

The primary database used was Medline (via PubMed). No limits were applied to the year of study, but only studies published in the English language were included. A thorough literature search was conducted, and was completed on April 11, 2019. The search strategy used: ("Sleep apnea"[TIAB] OR "Sleep apnoea" OR Sleep Apnea Syndromes[MeSH] OR "Sleep

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Table 1
Descriptions of included systematic reviews.

First author, year	Journal	Aims of SR: evaluation items (primary outcomes)	Number of included studies	Summary of Conclusions
Hoekema, 2004	Crit Rev Oral Biol Med.	Efficacy and side effects of OAm	13 (respectively)	OAm therapy is a viable treatment especially for mild to moderate OSA.
Lim, 2006	Cochrane Database Syst Rev.	Comparison between OAm and other treatments (daytime sleepiness, AHI)	17	There is increasing evidence suggesting that OAm improves subjective sleepiness and sleep disordered breathing. CPAP appears to be more effective in improving sleep disordered breathing than OAm.
Ahrens, 2010	Am J Orthod Dentofacial Orthop.	Efficacy of different OAms (the subjective patient-centered outcome)	14	There is no specific OAm design that most effectively influences the subjectively perceived treatment efficacy
Ahrens, 2011	Eur J Orthod.	Efficacy of different OAms (polysomnographic indices)	14	There is no specific OAm design that most effectively improves polysomnographic indices
Alsufyani, 2013	Sleep Breath.	Changes in the upper airway after therapy	3 on OAm	The available published studies provide evidence utilizing CBCT to measure anatomic airway changes post surgical and dental appliance treatment for OSA.
Iftikhar, 2013	J Clin Sleep Med.	Efficacy of OAm (blood pressure)	7	The pooled estimate shows a favorable effect of OAm on blood pressure.
Okuno, 2014	J Oral Rehabil.	Comparison between OAm and CPAP (AHI, ESS, arousal index lowest SpO2, SF-36)	5	OAm improves OSA when compared with untreated controls. CPAP appears to be more effective in improving OSA than OAm.
Guarda-Nardini, 2015	J Clin Sleep Med.	Predictive methods for the efficacy of OAm	13	The mandibular plane angle and the distance between hyoid bone and mandibular plane were found to have a predictive value for OAm effectiveness in OSA patients.
Saffer, 2015	Int Arch Otorhinolaryngol.	Predictive methods for the efficacy of OAm	14	It remains unclear which predictive factor can be used with confidence to select patients suitable for treatment with OAm.
Bratton, 2015	Lancet Respir Med.	Comparison between OAm and CPAP (ESS) [network meta-analysis]	13 on OAm	CPAP seemed to be a more effective treatment than OAm, and had an increasingly larger effect on more severe or sleepier OSA patients when compared with inactive controls.
Sharples, 2016	Sleep Med Rev.	Comparison between OAm and CPAP (AHI, ESS)	22 on OAm	CPAP is the most clinically effective treatment in reducing AHI in moderate to severe OSA.
Serra-Torres, 2016	Laryngoscope.	Efficacy of different OAms	22	Adjustable and custom-made OAms give better results than fixed and prefabricated appliances. Monobloc appliances cause more adverse effects.
Okuno, 2016	Sleep Med Rev.	Predictive methods for the efficacy of OAm	17	The predictive accuracy varied depending on the definitions of treatment success used as well as the type of index test.
Bartolucci, 2016	Sleep Breath.	Efficacy of different amounts of mandibular advancement	13	The AHI improvement was not proportional to the mandibular advancement increase.
Kastoer, 2016	J Clin Sleep Med.	Efficacy of remotely controlled mandibular positioner	4	Remotely controlled mandibular positioner might be a promising instrument for predicting OAm treatment outcome and targeting the degree of mandibular advancement needed.
Kuhn, 2017	Chest.	Comparison between OAm and CPAP (SF-36)	23	CPAP is effective in improving health-related QOL in OSA, and OAm may be just as effective, but further RCTs comparing the two treatments are required.
Iftikhar, 2017	Sleep Med.	Comparison between OAm and other treatments (AHI, ESS)	Total 80	CPAP is the most efficacious in complete resolution of sleep apnea and in improving the indices of saturation during sleep.
Cammaroto, 2017	Med Oral Patol Oral Cir Bucal.	Comparison between OAm and CPAP (AHI, ESS, lowest SpO2)	6	CPAP still must be considered the gold standard treatment for OSA and, therefore, OAm may be included in the list of alternative options.
Sivaramakrishnan, 2017	J Indian Prosthodont Soc.	Efficacy of different OAms	5	The results from this systematic review did not show significant advantages in using titratable appliances
Schwartz, 2018	Sleep Breath.	Comparison between OAm and CPAP (Sleepiness, AHI, QOL, usage compliance)	12	Though CPAP is significantly more efficient in reducing AHI (moderate quality of evidence), it has a significantly lower compliance resulting in no differences in QOLwith OAm, and no cognitive or functional outcomes.
de Vries, 2018	Sleep Med Rev.	Efficacy of OAm (cardiovascular outcomes)	11	It could be speculated that OAm may lead to a reduction in long-term cardiovascular morbidity and mortality in OSA patients.
Gao, 2018	J Formos Med Assoc.	Comparison between OAm and other minimally invasive treatments (AHI, ESS)	Total 89	Considering the effectiveness in reducing both AHI and ESS, CPAP was ranked the best, followed by OAm and positional therapy, while lifestyle modification alone was the least effective intervention.
Chen, 2018	J Oral Maxillofac Surg.	Changes in the upper airway after therapy (computational fluid dynamics analysis)	2 on Am	In the responders to OAm therapy, the velocity, wall static pressure, and airway resistance of the upper airway decreased. In nonresponders to OAm therapy, the wall static pressure and airway resistance of the upper airway increased.
Araie, 2018	Sleep Med Rev.	Side effects of OAm	21	Significant change of OJ, OB, and L1-MP was observed in patients with long-term OA use, while there were no significant changes of skeletal indices or mandibular rotation.
Zhang, 2018	Cranio.	Comparison between OAm and CPAP (AHI, lowest SpO2)	14	Even though CPAP can better decrease the severity of OSA, more patients opted for OAm, which showed better results in severe patients, especially adjustable OAm.
Martins, 2018	Dental Press J Orthod.	Side effects of OAm	6	The limited available evidence suggests that OAm therapy for snoring and OSA results in changes in craniofacial morphology that are predominantly dental in nature, especially on a long-term basis.
Bartolucci, 2019	Eur J Orthod.	Side effects of OAm	6	OAm therapy produces time-related dental and skeletal side effects.

AHI: apnea hypopnea index, CBCT: cone beam computed tomography, CPAP: nasal continuous positive airway pressure, ESS: Epworth Sleepiness Scale, OAm: mandibular advancement oral appliance, OSA: obstructive sleep apnea (including obstructive sleep apnea-hypopnea syndrome), OJ: over jet, OB: over bite, QOL: quality of life, RCT: randomized controlled trial.

apnea syndrome"[TIAB] OR "Sleep apnoea syndrome"[TIAB] OR "Sleep apnea hypopnea syndrome"[TIAB] "Sleep apnea, Obstructive"[MeSH] OR "Obstructive sleep apnea"[TIAB] OR "Obstructive sleep apnoea" OR "Obstructive sleep apnea syndrome"[TIAB] OR "Obstructive sleep apnoea syndrome"[TIAB] OR "Obstructive sleep apnea hypopnea syndrome"[TIAB] OR "Sleep disordered breathing"[TIAB] OR "Sleep related respiratory disorder"[TIAB] OR "Sleep respiratory disorder"[TIAB]) AND ("Oral appliance"[TIAB] OR "Oral device"[TIAB] OR "Oral splint"[TIAB] OR "Mandibular advancement appliance"[TIAB] OR "Mandibular advancement device"[TIAB] OR "Mandibular advancement splint"[TIAB] OR "Dental appliance"[TIAB] OR "Dental device"[TIAB] OR "Dental splint[TIAB] OR "Mandibular repositioning appliance"[TIAB] OR "Mandibular repositioning device"[TIAB] OR "Mandibular repositioning splint"[TIAB] OR "Prosthetic mandibular advancement"[TIAB] OR "Mandibular Advancement/instrumentation[MeSH]) AND ((Meta-Analysis[PT] OR meta-analysis[TIAB]) OR (Cochrane Database Syst Rev[TA] or systematic review[TIAB])). We searched through 50 articles, and excluded articles on pediatric subjects, treatments other than OA, and those written in languages other than English. We also excluded the articles, such as short communications, evidence reports, and clinical practice guidelines. There were some Cochrane reviews by Lim J et al., and an SR in 2006 [1] was not searched in this search strategy. However, we included this SR. Zhu et al. [2] included studies on OA, but not OAm. Liu et al. [3] did not describe the types of OA, and hence those SRs were excluded. Ultimately, 27 articles were included [1,4–29]. Descriptions of the included SRs are shown in Table 1. In 2016, Al-Jewair et al. [30] examined the methodological quality of the SRs and the meta-analyses (MA) on OA therapy. They concluded that the SRs on OA therapy for adult and pediatric sleep-disordered breathing'were conducted with an overall acceptable methodological quality.

Breakdown of the content of the 27 SRs is as follows: there were 10 articles on comparison with other treatments [1,9,12,13,18–20,22,24,27], five articles on the types of OAm [5,6,14,16,21], and six articles on the effect of OAm and the associated side effects [4,8,23,26,28,29]. There were also three articles on predicting the therapeutic effect of OAm [10,11,15], two articles on changes in the upper respiratory tract caused by this therapy [7,25], and one article on a remotely controlled mandibular positioner [17]. The SR by Okuno et al. [15] based on predicting the therapeutic effects of OAm was the latest. They concluded that the predictive accuracy varied depending on the definitions of treatment success used, as well as the type of index test.

2.2. Comparison with other treatments

The SRs on comparison of OAm with other treatments always included nasal continuous positive airway pressure (CPAP). OSA symptoms were set as study outcomes, and these included Apnea Hypopnea Index (AHI), Epworth Sleepiness Scale, and Quality of Life. Cross-over studies were also included; and hence, there were a large number of short-term studies. All the SRs stated that the CPAP was more effective than OAm with respect to the aforementioned outcomes. Cammaroto et al. [20] concluded that CPAP still must be considered the gold standard treatment for OSA, and OAm may be included in the list of alternative options. Kuhn et al. [18] examined the Quality of Life index and commented that CPAP was effective in achieving this outcome. They also carefully commented that investigation with a randomized controlled trial (RCT) was needed. Schwartz et al. [22] examined adherence, and analyzed that the usage time of CPAP is around one hour shorter than that of OAm. However, these results demonstrated a high degree of heterogeneity between studies.

CPAP and OAm are the two major conservative treatment options for OSA. We also reached the final conclusion that CPAP is superior to OAm in terms of improving OSA symptoms, as typified by the AHI. There is still room to investigate adherence. It is particularly essential to monitor the adherence of patients who have withdrawn from CPAP therapy, when they use OAm. On the other hand, in clinical practice, it is important to pursue the reason why patients are unable to use CPAP or OAm continuously, and take action to exclude the respective causes. Good adherence can be achieved within a few months.

2.3. Types of OAm

There are various types of OAm. OAm are broadly divided into two types: types with upper and lower jaws separated and types with fixed jaws. In Japan, when OA therapy is provided through the National Health Insurance, the fixed types of OAm are often used to balance the costs of the technician. In this review, we searched through five SRs on types of OAm. Ahrens investigated the subjective patient-centered outcomes [5] and polysomnographic indices [6]. They concluded that they were unable to demonstrate the most effective type of OA through both investigations. Serra-Torres et al. [14] concluded that adjustable and custom-made OAms give better results than fixed and prefabricated appliances; and monobloc appliances cause more adverse effects. However, this conclusion was their interpretation of the included observational studies. Sivaramakrishnan and Sridharan [21] compared the titratable OAm with the fixed non-titratable OAm. He included five studies. Four of the five studies were observational, and one was a short-term cross-over randomized trial. There was a high degree of heterogeneity between the study results, so they did not conduct a meta-analysis. Therefore, they concluded that "This SR does not demonstrate significant advantages in using titratable appliances". This field has many unresolved questions. It is essential to investigate adherence in addition to improvement of OSA symptoms, typified by the AHI. It is also necessary to investigate the long-term dental and skeletal side effects.

OAm positions the lower jaw anteriorly, thereby improving upper respiratory tract obstruction. Bartolucci et al. [16] investigated the anterior positioning of the lower jaw. They included RCT data to analyze the ratio of the maximum possible distance of anterior movement and improvement rate of AHI, using a bubble plot. They concluded that the improvement in the AHI was not proportional to the increase in mandibular advancement. We also found that the appropriate position of the lower jaw is not uniform, and it differs depending upon the individual. However, in Japan, where the fixed OAm (non-titratable, but adjustable OAm) is mainstream, it is worthwhile to provide dentists with an indication of the initial position of the mandible.

2.4. Effect of OAm and side effects

An important outcome of OSA treatment is prevention of complications typified by cardiovascular disease, and reducing the mortality associated with these complications. This outcome is more important for severe cases of OSA. Mild cases also require caution with increase in the baseline of AHI caused by aging and weight gain. There are two SRs on improvement of cardiovascular disease [8,23]. Iftikhar et al. [8] evaluated blood pressure, and concluded that the pooled estimate shows a favorable effect of OAm on blood pressure. However, he also stated that almost all the data came from observational studies. Five years later, de Vries et al. [23] evaluated the cardiovascular effects. All the RCTs had a follow-up period of three months, which was considered to be too short. De Vries et al. [23] also commented that one study [31] showed that OAm was as effective as CPAP in reducing death from a cardiovascular cause, but that study was not an RCT, and it probably had selection bias. We believe using a propensity score

and conducting a long-term observational study with a carefully designed OAm could resolve this question.

The SR by Hoekema et al. [4] was the first one on OAm. They compared OAm with other treatments, conducted a meta-analysis on evaluation of the type of device, and also evaluated side effects. After that, there were no SRs published on side effects for some time. Patients can tolerate many short-term side effects. However, there are irreversible side effects among those that occur over the long-term. There has been an increase in the number of studies with longer study periods. An SR on long-term side effects has recently been published [26,28,29]. There were differences in the number of studies included in the three SRs. The reason for this is that Martins et al. [28] included RCTs only. There were differences in the studies included by Araie et al. [26] and Bartolucci et al. [29] because of the search date, and Bartolucci et al. [29] only targeted studies where OAm was used for two or more years. The interpretation of the studies differed among the three SRs. For example, the study by Ringqvist et al. [32] was included as an RCT by Martins et al. [28], and as a non-randomized study by Araie et al. [26]. However, it was not included at all by Bartolucci et al. [29]. Either way, morphological changes in the teeth and skeleton were seen over the long-term (Araie et al. [26] stated that there were no changes in skeletal indices or mandibular rotation). Bartolucci et al. [29] used a bubble plot, and concluded that OAm therapy produces time-related dental and skeletal side effects.

Araie et al. [26], stated the importance of clinicians being aware of the side effects. We also emphasize on the duty of dentists to explain the long-term side effects to patients at their initial visit to the clinic. It is vital to deal with these side effects at an early stage. One of the long-term side effects is posterior open bite. Reports indicate that 70% of the patients are unaware of this symptom [33]. The extent of awareness of masticatory disturbances and cosmetic disturbances caused by dental and skeletal side effects differs depending on the patient. Dentists must respond to these long-term side effects on a case-by-case basis. Regular persistent follow-up monitoring is important. Among the SRs included in this study, none investigated long-term adherence. We confirmed this situation in our hospital and also investigated the situation in the studies included in the SRs. In particular, we investigated the examinations conducted by dentists, namely follow-up monitoring.

3. Consultation rate for follow-up: at our hospital and in literature

3.1. Current situation in our hospital

Here we report the current situation in our hospital (Ichikawa General Hospital, Tokyo Dental College). The dentists in this hospital have been treating patients diagnosed with OSA by the division of otolaryngology of this hospital or another hospital with fixed OAm since 1999. The position of the lower jaw was adjusted referencing subjective symptoms or sleep tests. Follow-up monitoring was started once the patient was free of discomfort, and the effect of the device has been confirmed using sleep tests. The longest duration of follow-up monitoring was set as six months. The medical consultation situation was checked every two months, and we contacted patients who had discontinued consultations by telephone. Patients who had not had a medical consultation for one year or more, despite repeated telephone calls, were considered to have discontinued treatment (dropout case).

We surveyed patients who had received OAm therapy in the one-year period between June 2015 and May 2016 (in-hospital ethics review number: I 16–48). The consultation situation of the patients during this period was checked up to February 2019. There were 46 patients in total. Five patients were unable to continue use due to inability to get used to the device or jaw pain. Two patients discontinued treatment due to relocation, and one patient switched to CPAP. OAm therapy was started in the remaining 38 patients, but eight patients stopped reporting for consultations before the sleep test. Approximately 20% of the patients refused to undergo the test to confirm the effect. One patient was found not to have any effect from the sleep test. Finally, 29 patients had the effect of the treatment confirmed with a sleep test, and follow-up monitoring was started for them. Seven of these patients discontinued consultations. During the approximate three years of follow-up monitoring, one in four patients discontinued consultations. Some patients who discontinued consultations are still using OAm. Hence, this value is the percentage of patients who continued consultation, and not the percentage of those who continued to use OAm.

3.2. Consultation rate in the literature

We used the studies included in the SRs that investigated long-term side effects [26,28,29]. Doff et al. conducted an RCT comparing OAm with CPAP, and reported the results in multiple articles. We checked the Flow diagram by Doff et al. [34]. Seven of the 51 patients who switched to CPAP partway through the study; hence, 44 patients were treated with OAm. Two patients were lost to follow-up in the first two months, and one patient was lost to follow-up by the end of the study, two years later. This good result achieved in their study demonstrates a bias of the cases participating in the RCT. We examined the prospective observational studies included by Araie et al. [26] and Bartolucci et al. [29]. Fransson et al. [35] reported that 12 out of 77 patients (15.6%) discontinued treatment of their own accord during the two-year observation period. Hou et al. [36] reported that 27 out of 151 patients (17.9%) failed to attend follow-up appointments in the three-year observation period. Martínez-Gomis et al. [37] reported that nine out of 40 patients (22.5%) discontinued treatment of their own accord during the five-year observation period. Sharples et al. [38] summarized an investigative report on clinical effectiveness and cost-effectiveness. This was one of the articles excluded from this review. They introduced a French cohort with a 76% usage rate (not consultation rate) over 2.75 years [39].

The aforementioned data are from the facilities that conducted the research. We estimate that 20–25% of patients stop coming for consultations (including patients still using the device) when OAm therapy is continued for approximately three years in these facilities.

4. Conclusions

4.1. Summary to date

- CPAP is superior to OA in improving OSA symptoms.
- It is necessary to survey the adherence to OAm therapy of patients who stopped CPAP therapy.
- There is little evidence supporting the theory that OAm therapy prevents cardiovascular disease or improves life prognosis.
- OAm therapy has dental and skeletal side effects with long-term use.
- There is still room to investigate the types of OAm. It is particularly essential to investigate adherence and side effects after starting follow-up monitoring (once the effect of OAm has been confirmed).
- A certain percentage of patients discontinue consultations.

4.2. Expectations from clinic-based dentists involved in OAm therapy

The clear results are: superiority of CPAP and dental and skeletal side effects of OAm. The latter is especially important for dentists. Long-term follow-up monitoring by dentists is important to deal with this side effects of OAm and worsening of the OSA baseline. This review has reiterated the importance not only of long-term use of the device by patients, but also the importance of reporting for consultations at a medical institution, and being examined by dentists. However, there are a certain number of patients who hesitate to visit general hospitals or dental hospitals. One of the reasons for this is that a large number of the patients are middle-aged men who work during the day. Clinics are easier to attend than hospitals. We believe that providing OAm therapy in a clinic could improve the continuing consultation rate. OAm requires adjustment when patients are treated with dental prosthetics. From this perspective, there are advantages in the clinic-based dentists treating patients with OAm. The maintenance interval for periodontitis is also the ideal interval for follow-up monitoring of OA therapy. Although the purpose of this review was to provide the current evidence of OAm for clinic-based dentists, this review also proves the benefit of dental clinic-based OAm therapy.

On the other hand, the American Academy of Sleep Medicine and the American Academy of Dental Sleep Medicine created a clinical practice guideline in 2015 [40]. This clinical practice guideline recommends that follow-up monitoring is to be continued appropriately by sleep physicians and qualified dentists. It is important to foster dentists who are able to deal with sleep medicine, which includes conducting medical examinations in collaboration with sleep physicians. Enhancing under-graduate and post-graduate education on sleep medicine, and establishing a specialist system are strategies for fostering the ability of dentists to handle OAm therapy in dental clinics. On the other hand, OAm places a burden on the teeth and the jaws. Searching for an alternative therapy is the duty of dentists. We anticipate that increasing the number of dentists involved in sleep medicine will result in the creation of new ideas for an alternative therapy.

Conflicts of interest and source of funding

There are no conflicts of interest to declare. No funding was acquired for this study.

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