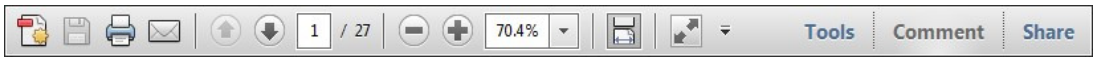
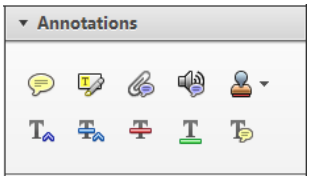
Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

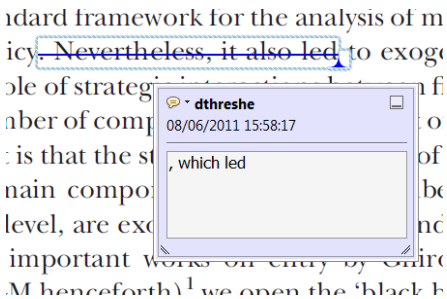


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

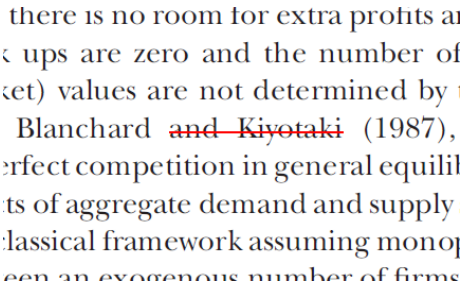


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

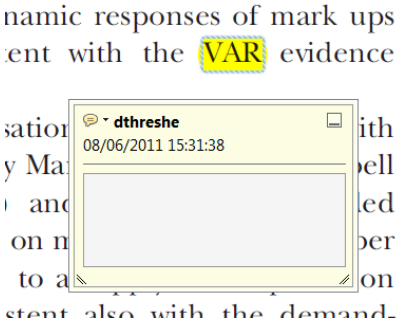


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

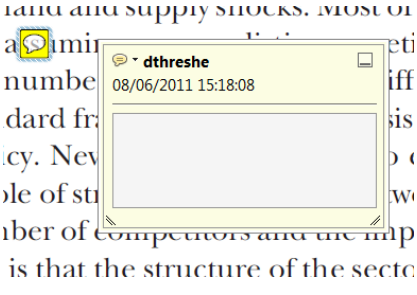


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

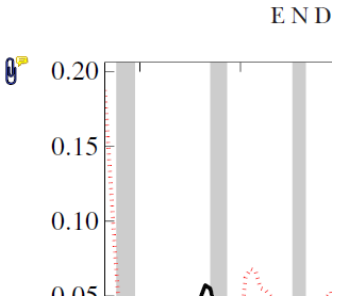


5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate place in the text.

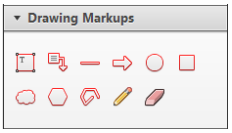
How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.



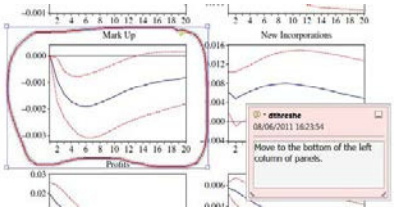
6. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



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ORIGINAL ARTICLE

A 2-year mean follow-up of oral appliance therapy for severe obstructive sleep apnea: a cohort study

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OBJECTIVE: Oral appliances for treating severe obstructive sleep apnea (OSA) are recommended for patients who failed to comply with continuous positive airway pressure (CPAP) treatment. The objective of this study was to evaluate medium long-term outcome and success rates of oral appliances in patients with severe OSA.

METHODS: In a retrospective study, 52 OSA patients with an apnea–hypopnea index (AHI) ≥40, who did not tolerate CPAP treatment, were enrolled and fitted with a modified Herbst oral appliance. A 2-year mean follow-up including a second somnography was conducted in 36 of the patients.

RESULTS: A significant reduction ($P < 0.0001$) in the AHI was demonstrated between the initial somnography (55.25 ± 10.79,) and the followed one (17.74 ± 11.0, $n = 36$). Overall, 57.7% of total study subjects ($n = 52$) and 63.9% ($n = 36$) that had sequential sonmogarphy continued using the device. The reduction in AHI in the user group was 42.4 ± 3.1 ($n = 23$), which was significantly higher ($P = 0.013$) than in the non-user group (28.9 ± 17.2; $n = 13$). Moreover, 53% ($n = 19$) reached AHI of <15.

CONCLUSIONS: Oral appliances were found to be successful for treating for severe OSA after first-line treatment had failed.

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Keywords: obstructive sleep apnea; oral appliance; dental appliance; continuous positive airway pressure; apnea hypopnea index

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Introduction

Obstructive sleep apnea (OSA) syndrome is characterized by frequent repetitive events of full (apnea) or partial (hypopnea) collapse and blockage of the upper airway for at least 10 s during sleep, often leading to a drop in oxygen saturation and usually followed by a microarousal (Huang *et al*, 1995; Horner, 2008; Azagra-Calero *et al*, 2012). Patients are aware of only a small fraction of these obstructions and awakenings. Symptoms include loud snoring, choking and gasping for air during sleep, and/or daily tiredness, and/or morning headaches (Headache Classification Subcommittee of the International Headache Society, 2004). High body mass index (BMI) is a major risk factor (Garg *et al*, 2012). Polysomnography, a nighttime laboratory sleep test, is the standard method of diagnosis of OSA (Iber *et al*, 2007). It yields the apnea–hypopnea index (AHI) (Young *et al*, 2002) which is calculated by summing the average number of apnea and hypopnea events per hour of sleep. The American Sleep Disorder Association (The Report of an American Academy of Sleep Medicine Task Force, 1999) categorized OSA based on the AHI, as follows: normal sleep, AHI <5; mild OSA, AHI 5–15; moderate OSA, AHI 15–30; severe OSA, AHI >30. OSA, especially severe OSA, has been associated with cardiovascular morbidity (Marin *et al*, 2005), systemic hypertension (Young *et al*, 2002; O'Connor *et al*, 2009), cerebrovascular disorders (Gibson, 2004), and depression (Baran and Richert, 2003). Patients may report a considerable reduction in overall quality of life (Phillips *et al*, 2013). Some studies noted a higher rate of early death in patients with OSA (Yaggi *et al*, 2005; Won *et al*, 2006) and a higher-than-normal rate of fatal road accidents (Horne and Reyner, 1995).

Continuous positive airway pressure (CPAP) is the first-line treatment for severe OSA (Sullivan *et al*, 1981). It has been found to reduce the risk of cardiovascular morbidity (Cloward *et al*, 2003; Buchner *et al*, 2007; Thomas and Ren, 2012) and improve quality of life (Giles *et al*, 2006; Avlonitou *et al*, 2012). However, it is limited by poor patient adaptation and habituation (Kribbs *et al*, 1993; Grunstein, 1995; Weaver and Grunstein, 2008),

resulting in a major health risk necessitating additional modes of therapy. As a result, attention has focused on removable oral appliances that can be worn during sleep (Cistulli *et al*, 2004; Ferguson *et al*, 2006; Chan *et al*, 2007; Huynh *et al*, 2014).

The most popular are devices that fit onto the dental arches and move the mandible forward, thereby moving the tongue from the back of the throat and widening the oropharyngeal space, preventing its collapse during sleep. Although studies have documented improvements in all OSA-related comorbidities with the use of oral appliances, they are still considered inferior to CPAP (Clark *et al*, 1996; Ferguson *et al*, 1997; Engleman *et al*, 2002; Randerath *et al*, 2002; Barnes *et al*, 2004; Lim *et al*, 2006; Li *et al*, 2013). According to the American Academy of Sleep Medicine treatment guidelines (Kushida *et al*, 2006), oral appliances should currently be considered for patients with snoring without OSA and patients with OSA of minor to moderate severity or serve as an alternative to CPAP in non-compliant patients in severe OSA. However, long-term outcome and success rates of oral appliances in patients with severe OSA have hardly been evaluated systematically in polysomnography studies. The aim of this study was to close this gap. We also sought to determine whether oral appliances can provide a long-lasting solution for these patients.

Materials and methods

Study setting and design

A retrospective study design was used. The databases of a dental sleep medicine center and two associated sleep laboratories in Israel were collected from January 2006 to June 2012 for patients diagnosed with very severe OSA (AHI ≥40) who did not tolerate CPAP and were referred for treatment with an oral appliance. IRB approval was established from Barzilai Medical Center (No. BRZ-0111-13).

Exclusion criteria were a history of temporomandibular disorder (muscle – or temporomandibular joint-oriented) and incomplete follow-up.

Study protocol

Patients underwent a sleep test scored according to accepted criteria (Iber *et al*, 2007), followed by an examination by an otolaryngologist who referred them for evaluation by a dentist specializing in dental devices. Patients were informed of the health risks of severe OSA and about other treatment possibilities. They received a detailed explanation of the application of the oral appliance for sleep apnea and signed an informed consent form. A modified removable Herbst mandibular repositioning device (Rider, 1988; Schiavoni, 2011) (Dentarum, Germany) was used in all cases tailored to the individual patient. The device consists of upper and lower acrylic components attached by a laterolateral plunger mechanism that pulls the mandible forward during sleep. A raised 0.6- to 1-cm protrusive bite registration was taken. The degree of mandibular advancement when was fixed at 50–75% of maximum mandibular protrusion and titrated to the position at which the patient reported improvement in daytime sleepiness or the bed partner reported a considerable reduction in snoring. Two to four adjustment meetings were conducted over the study period, after which, the patient was referred back to have a follow-up sleep test with the appliance.

Data collection

Data on background variables and the results of the sleep tests were collected from the patients' files. Patients were routinely contacted by telephone and questioned about the effectiveness of the appliance in terms of snoring (by report of the sleep partner), daily tiredness, and subjective side effects. Outcome was compared between patients who used the oral appliance throughout follow-up and those who stopped its use before the end of the study period. The end of the follow-up was defined as the last telephone contact in June 2012 or treatment discontinuation as noted in our medical records (Figure 1).

Statistical analysis

Data were tabulated and analyzed using SPSS 19 (for Macintosh). Alpha for significance was set at 5%. The distribution of both sets of AHI data was normal (one-sample Kolmogorov–Smirnov test, $P = 0.35$ and $P = 0.58$ for the first and second set, respectively). Therefore, a paired *t*-test was used to analyze the difference in mean AHI from the first (pre-appliance) to the second (with the appliance) sleep test, and an unpaired *t*-test was used to compare the change in AHI from the first to the second sleep test between patients who used the appliance to the end of the study and those who did not. Regression analysis was applied to examine the relationship between patient characteristics and the change in AHI from the first to the second sleep test. The proportion of patients still using the

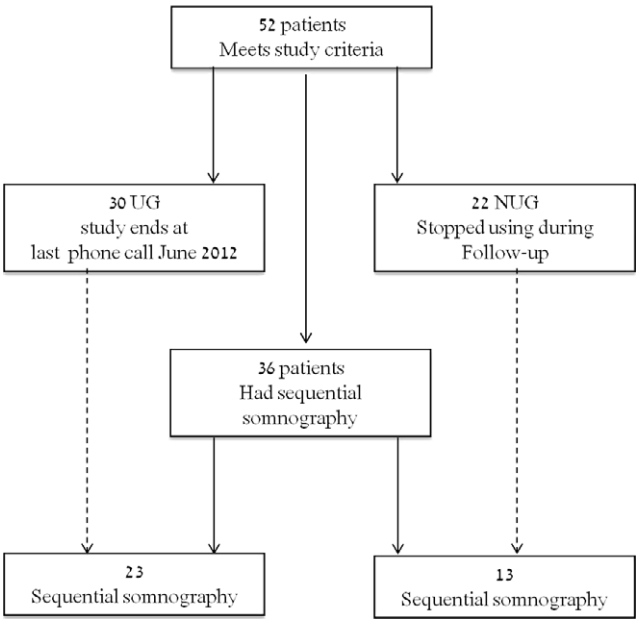


Figure 1 Flow chart of methods and follow-up period. UG, users group; NUG, non-users group

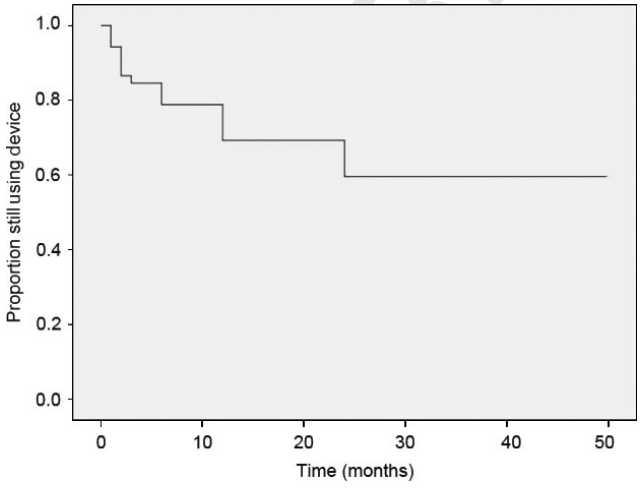
device at the end of the study period was depicted with a Kaplan–Meier plot.

Results

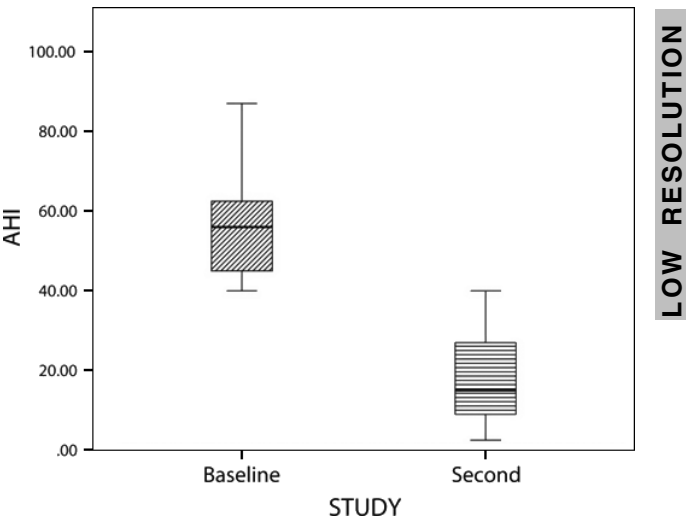
Of the 64 patients with severe OSA identified by our database search, 52 met the study criteria. They included 48 male and four female patients of mean age 56.75 ± 2.09 years (range, 28–82) and mean BMI 29.47 ± 4.19 kg m^{-2} (range, 23.35–42.01). The mean duration of follow-up was 24 months (range, 5–76 months) (Figure 2). Thirty patients (57.7%) reported using the device to the end of the study period and 22 (42.3%) stopped before that. The mean duration of follow-up for these subgroups was 44 months (range 5–76 months) and 9 months (range, 1 day–24 months), respectively.

Thirty-six of the 52 patients underwent a second sleep test (with the oral device) and 16 did not (baseline sleep test only), mainly for insurance reasons. Analysis of the patients who had a sequential test revealed a mean AHI of 55.3 ± 10.8 on the first on and 17.7 ± 11.0 on the second, with a mean reduction (ΔAHI) of 37.5 ± 15.8. The difference in AHI between the tests was statistically significant (paired *t*-test: $t = 14.157$, df = 35, $P < 0.0001$; Figure 3). The AHI on the second sleep test was <15 (mild or no OSA) in more than half the patients ($n = 19$, 53%), of which four had an AHI <5 (11.1%). Of the remainder, 13 (36%) had an AHI of 15–30 (moderate OSA) and 4 (11%) had an AHI of ≥30. Of the 36 patients who underwent a second sleep test, 23 used the device throughout the study and 13 stopped its use. The decrease in mean AHI from the first to the second test was significantly greater in the patients who used the device throughout (**Δ**AHI 42.4 ± 13.1 *vs* 28.9 ± 17.2, respectively; paired *t*-test: $t = -2.634$, df = 34, $P = 0.013$; Figure 4). Moreover, no differences were found in gender, age, BMI, and primary AHI between patients who continued using the device and those who did not.

LOW RESOLUTION FIG

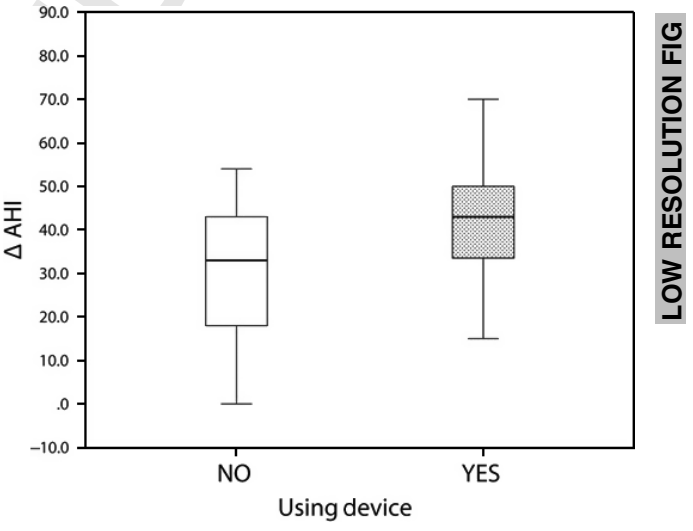


13 **Figure 2** Treatment protocol. Chart demonstrating follow-up from delivery of the oral appliance to interview day (end of study) or until patients discontinued using the appliance



LOW RESOLUTION

14 **Figure 3** Change in AHI with appliance use. Significant reduction in AHI between initial (pre-appliance) and second (with the appliance) sleep test. AHI, apnea–hypopnea index

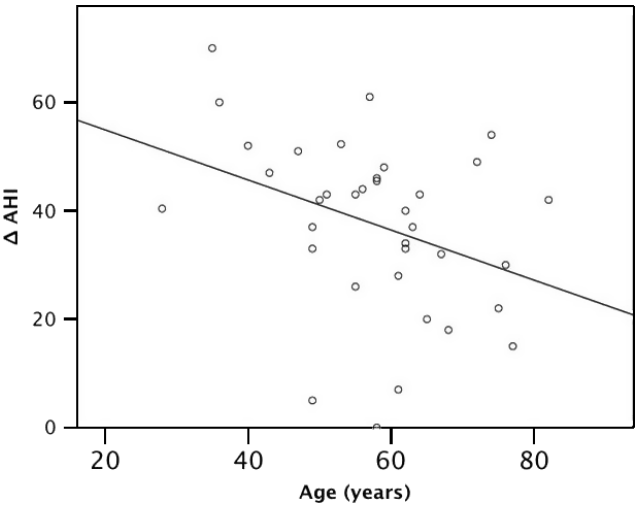


LOW RESOLUTION FIG

15 **Figure 4** Outcome by compliance with appliance use. The difference in AHI from the first to the second sleep test (ΔAHI) is higher in patients still using the appliance (yes) at the end of the study than in patients who stopped using it (no). AHI, apnea–hypopnea index

Patients who did not undergo a second sleep test presented with similar profiles to those who had a second sleep test, with a mean age of 54.6 ± 18, primary AHI of 55.8 ± 14.4, BMI of 30.1 ± 5.2, and a follow-up period of 44.1 ± 19.8 months. The only factor that was different was the compliance rate, which was 43.7% for the group that did not have a second sleep test compared with 63.9% for those that did.

Analysis of the background factors in relation to the change in AHI revealed that the appliance was more effective in younger patients ($R^2 = 0.129$; Figure 5). BMI was positively correlated with the AHI value in the baseline polysomnography test but not in the sequential one (data not shown).



16 **Figure 5** Effect of age. Younger patients showed a greater change in apnea–hypopnea index from the first to the second sleep test than older ones

Regarding compliance and subjective efficacy, the 52 patients that met study criteria were divided into two groups – patients who continued using the device until the final phone call (users group = UG) and patients who discontinued using the device before the final phone call (non-users group = NUG). Thirty patients (57%, $n = 52$) used the appliance to the end of follow-up (UG), 23 of whom (77.0%, or 43.0% of the whole cohort) reported doing so every night, 4 (13.0%, or 7.7% of the whole cohort) used it 1–5 nights per week, and 3 (10.0%, or 5.8% of the whole cohort) used it only when traveling (Table 1). Regarding the subjective benefit, 26 patients (86.6%) reported both less snoring and less daily tiredness and 3 (10.0%) reported less snoring only; the responses of one patient (3.3%) were uninformative. Of the 22 (43% $n = 52$) patients who stopped using the device during the study period, 10 (45.6%) reported both less snoring and improved daily tiredness, 1 (4.5%) reported less snoring, and 5 (22.6%) reported no improvement; the responses of six patients (27.3%) were uninformative (Table 2). Questions referred to the time that the dental device was in use. The main reasons for discontinuing use of the appliance were regular dental treatment followed by the lack of adjustment of the device and the lack of sufficient effectiveness. No major side effects of the appliance were reported.

Discussion

Previous studies reported higher success rates of oral appliances in OSA patients with lower AHI values (Menn *et al*, 1996; Pancer *et al*, 1999; Lowe *et al*, 2000; Neill *et al*, 2002; Randerath *et al*, 2002; Rose *et al*, 2002; Kushida *et al*, 2006). The place of oral appliances in the therapeutic armamentarium of severe OSA remains unclear and therefore was the focus of this study. In the literature, success rates among patients with severe OSA range widely, from 14% to 61% (Barthlen *et al*, 2000; Lowe *et al*, 2000; Lam *et al*, 2011), at least partly because of differences in the definition of success and failure among the studies. The strictest definition of success is a final AHI of <5 (Henke *et al*, 2000; Engleman *et al*, 2002; Johnston *et al*, 2002), which is considered normal breathing by the American Sleep Disorder Association (Report of an American Academy of Sleep Medicine Task Force, 1999). Some studies use an AHI of <10 (Clark *et al*, 1996) or <15 (Lowe *et al*, 2000) to define success. The most tolerant definition is an improvement in AHI of 50% compared with the initial AHI (Ishida *et al*, 1999; Barthlen *et al*, 2000; Henke *et al*, 2000; Johnston *et al*, 2002). Furthermore, most of the studies did not focus specifically on severe OSA, and few followed patients for an adequate length of time.

In the present study, we evaluated the outcome of patients with severe OSA who were referred for treatment with an oral appliance after failure of CPAP. We focused on a subgroup of patients with very severe OSA to demonstrate the dental device efficacy in extreme cases of the disease. We therefore restricted our cohort to those who were diagnosed with AHI of over 40 although severe OSA is defined as AHI >30.

We found that in the patients who underwent a polysomnography test (with the appliance), mean AHI decreased markedly, from 55.2 at the first (pre-appliance test) to 17.3 ($P = 0.002$). In 89% of patients, the AHI dropped to the level of moderate OSA (36%) to mild OSA/normal night breathing (53%). These results provide objective evidence of the effectiveness of the oral appliance in alleviating severe OSA. While success or efficacy is sometimes relative, with 50% improvement being a major benefit to the patient as regards quality of life, this may not be enough to prevent the morbidity associated with sleep apnea. The objective results were supported by the subjective outcome, as assessed by telephone interview conducted on average 24 months after delivery of the device. Overall, almost 77% reported a decrease in snoring alone or together with daytime tiredness.

Oral appliances are considered a permanent treatment modality in OSA, and therefore, it is essential that follow-up is long enough to properly evaluate compliance and outcome. Most compliance studies use questionnaires sent by mail with an only moderate response of around 40% (de Almeida *et al*, 2005, Jauhar *et al*, 2008). Here, the authors located and contacted 52 of a total of 64 patients (81%), so minimizing any skewing of results due to lack of response from those who were no longer complying.

In the present study, the mean duration of follow-up was 24 months, ranging from 5 to 76 months (6.4 years). More than half the patients (57.7%, $n = 52$) continued using the device over this time (77.0% every night, by self-report). Patients who had a second somnography had

Table 1 Oral appliance usage. Oral appliance use frequency characteristics within user group (UG) – 30 of 52 patients

Use of oral appliance (n = 52)	*Every night*	*1–5 nights per week*	*Only while traveling*
% patients	44.2	7.7	5.8
% UG	77.0	13.0	10.0
n	23	4	3

Table 2 Subjective improvement with use of oral appliance (n = 52). Subjective assessment regarding oral appliance efficacy in user group (UG) in terms of snoring and daily tiredness compared with non-users group (NUG)

Subjective improvement	*Snoring and day tiredness*	*Only snoring*	*Did not know*	*None*
UG (n = 30)	86.6% (n = 26)	10% (n = 3)	3.3% (n = 1)	0
NUG (n = 22)	45.6% (n = 10)	4.5% (n = 1)	27.7% (n = 6)	22.6% (n = 5)

a 63.9% (n = 36) compliance rate. Previous studies of patients with mild to moderate OSA noted a similar rate of use at 1 year (Ferguson *et al*, 2006), with a decline to 50% at 3 years (Clark *et al*, 2000). A 10-year follow-up study of 180 patients observed a 65% compliance rate, with OSA severity having no significant effect on use over time (Jauhar *et al*, 2008). Care must be taken in the interpretation of this last study because only 40% of the patients returned completed questionnaires.

We found that patients who used the appliance to the end of the follow-up period did significantly better in terms of the decrease in AHI (mean **Δ**AHI 42.4) than those who did not (mean **Δ**AHI 28.9). Some patients had to discontinue use for unrelated reasons (such as dental care). In the others, whether the better outcome encouraged their better compliance with the device or the continued use led to a better outcome is unclear.

In our study, younger age was significantly associated with better treatment response, in concordance with previous studies (Randerath *et al*, 2002; Kushida *et al*, 2006; Krishnan *et al*, 2008). This factor should be considered in assessing the potential success of oral appliance therapy. BMI was not related to treatment outcome. Overall, the correlation between oral appliance therapy success and BMI is disputed in the literature. A recent 10-year follow-up study (Chen and Lowe, 2013) found no effect of BMI on treatment success, whereas others observed that high BMI is a negative predictor of OSA improvement with oral appliance therapy (Marklund *et al*, 2004; Tsuiki *et al*, 2013).

A second BMI measurement was not made; therefore, we cannot rule out the possibility that weight loss influenced the results. Nevertheless, primary improvement of sleep may act on hunger pathways via the ghrelin hormone (Takahashi *et al*, 2008), as well as on satiety hormones such as leptin (Zhang *et al*, 2014) and so lead to weight loss with its added beneficial effect.

The role of background and clinical factors in the success rate of oral appliances for OSA warrants further study.

This study was limited by the retrospective design, the collection of data from different patients at different time intervals, and the wide range of follow-up. Not all patients underwent a second polysomnography test with the appliance, although this may be representative of the majority of clinics dealing with patients with OSA (de Almeida *et al*, 2005). Also, compliance rate was lower in patients who did not undergo a second sleep test, probably due to lack of motivation. In addition, the titration protocol was based primarily on the patients'/partners' subjective assessment. It would be interesting to determine whether greater protrusion of the lower jaw will lead to even higher success rates for the appliance.

Our sample was restricted to patients who had failed to adjust to first-line treatment with CPAP. This factor may have had an effect on their general acceptance and compliance with second-line treatment. More information on personality characteristics of patients could have been helpful for understanding the reasons for non-compliancy. Clear subjective improvement, however, especially in terms of reduced daily sleepiness, encourages people to continue to use the device. Additional research is needed to identify the specific type and design of oral appliance that induces the best compliance over time (Ahrens *et al*, 2010) and the potentially important role of close and regular physician follow-up to help patients cope with problems that may occur, such as dental treatments that may interfere with the fit of the device.

Further studies are needed to find predictors of oral appliance therapy outcome – compliance and efficacy. Also there is a need to determine whether the subjective and objective improvement is in correlation with medical status and co morbidities associate with OSA.

Conclusions

This study focused on oral appliance therapy for the most severe degree of OSA, with long-term follow-up (2 years). The results show that the oral appliance has good potential for success after first-line treatment has failed in severe and extremely severe sleep apnea. Compliance over time was moderate. Further efforts should be invested in further improving the success and compliance rates of oral appliances because of the important implications to this complicated group of patients.

Acknowledgements

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Author contribution

Y. Haviv made substantial contributions to the study's conception and design, acquisition of data, and analysis and interpretation of data; drafted the submitted article and provided final approval of the version to be published. G. Bachar conducted the study and wrote the draft. D. J. Aframian, G. Almoznino and E. Michaeli revised and approved the manuscript. R. Benoliel analyzed the data and approved the manuscript.

References

(1999). Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* **22**: 667–689.

(2004). The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* **24**(Suppl. 1): 9–160.

Ahrens A, McGrath C, Hagg U (2010). Subjective efficacy of oral appliance design features in the management of obstructive sleep apnea: a systematic review. *Am J Orthod Dentofac Orthop* **138**: 559–576.

de Almeida FR, Lowe AA, Tsuiki S *et al* (2005). Long-term compliance and side effects of oral appliances used for the treatment of snoring and obstructive sleep apnea syndrome. *J Clin Sleep Med* **1**: 143–152.

Avlonitou E, Kapsimalis F, Varouchakis G, Vardavas CI, Behrakis P (2012). Adherence to CPAP therapy improves quality of life and reduces symptoms among obstructive sleep apnea syndrome patients. *Sleep Breath* **16**: 563–569.

Azagra-Calero E, Espinar-Escalona E, Barrera-Mora JM, Llamas-Carreras JM, Solano-Reina E (2012). Obstructive sleep apnea syndrome (OSAS). Review of the literature. *Med Oral Patol Oral Cir Bucal* **17**: e925–e929.

Baran AS, Richert AC (2003). Obstructive sleep apnea and depression. *CNS Spectr* **8**: 128–134.

Barnes M, McEvoy RD, Banks S *et al* (2004). Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med* **170**: 656–664.

Barthlen GM, Brown LK, Wiland MR, Sadeh JS, Patwari J, Zimmerman M (2000). Comparison of three oral appliances for treatment of severe obstructive sleep apnea syndrome. *Sleep Med* **1**: 299–305.

Buchner NJ, Sanner BM, Borgel J, Rump LC (2007). Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *Am J Respir Crit Care Med* **176**: 1274–1280.

Chan AS, Lee RW, Cistulli PA (2007). Dental appliance treatment for obstructive sleep apnea. *Chest* **132**: 693–699.

Chen H, Lowe AA (2013). Updates in oral appliance therapy for snoring and obstructive sleep apnea. *Sleep Breath* **17**: 473–486.

Cistulli PA, Gotsopoulos H, Marklund M, Lowe AA (2004). Treatment of snoring and obstructive sleep apnea with mandibular repositioning appliances. *Sleep Med Rev* **8**: 443–457.

Clark GT, Blumenfeld I, Yoffe N, Peled E, Lavie P (1996). A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. *Chest* **109**: 1477–1483.

Clark GT, Sohn JW, Hong CN (2000). Treating obstructive sleep apnea and snoring: assessment of an anterior mandibular positioning device. *J Am Dent Assoc* **131**: 765–771.

Cloward TV, Walker JM, Farney RJ, Anderson JL (2003). Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. *Chest* **124**: 594–601.

Engleman HM, McDonald JP, Graham D *et al* (2002). Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* **166**: 855–859.

Ferguson KA, Ono T, Lowe AA, al-Majed S, Love LL, Fleetham JA (1997). A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. *Thorax* **52**: 362–368.

Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W (2006). Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* **29**: 244–262.

Garg R, Singh A, Prasad R, Saheer S, Jabeed P, Verma R (2012). A comparative study on the clinical and polysomnographic pattern of obstructive sleep apnea among obese and non-obese subjects. *Ann Thorac Med* **7**: 26–30.

Gibson GJ (2004). Sleep disordered breathing and the outcome of stroke. *Thorax* **59**: 361–363.

Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ (2006). Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* ?????: CD001106. **7**

Grunstein RR (1995). Sleep-related breathing disorders. 5. Nasal continuous positive airway pressure treatment for obstructive sleep apnoea. *Thorax* **50**: 1106–1113.

Henke KG, Frantz DE, Kuna ST (2000). An oral elastic mandibular advancement device for obstructive sleep apnea. *Am J Respir Crit Care Med* **161**: 420–425.

Horne JA, Reyner LA (1995). Sleep related vehicle accidents. *BMJ* **310**: 565–567.

Horner RL (2008). Pathophysiology of obstructive sleep apnea. *J Cardiopulm Rehabil Prev* **28**: 289–298.

Huang L, Quinn SJ, Ellis PD, Williams JE (1995). Biomechanics of snoring. *Endeavour* **19**: 96–100.

Huynh NT, Emami E, Helman JI, Chervin RD (2014). Interactions between sleep disorders and oral diseases. *Oral Dis* **20**: 236–245.

Iber C, Ancoli-Israel S, Chesson A, Quan SF (2007). *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. American Academy of Sleep Medicine: Westchester, IL.

Ishida M, Inoue Y, Okamoto K *et al* (1999). Clinical efficacy of prosthetic mandibular advancement on obstructive sleep apnea syndrome. *Psychiatry Clin Neurosci* **53**: 323–325.

Jauhar S, Lyons MF, Banham SW, Cameron DA, Orchardson R (2008). Ten-year follow-up of mandibular advancement devices for the management of snoring and sleep apnea. *J Prosthet Dent* **99**: 314–321.

Johnston CD, Gleadhill IC, Cinnamond MJ, Gabbey J, Burden DJ (2002). Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial. *Eur J Orthod* **24**: 251–262.

Kribbs NB, Pack AI, Kline LR *et al* (1993). Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* **147**: 887–895.

Krishnan V, Collop NA, Scherr SC (2008). An evaluation of a titration strategy for prescription of oral appliances for obstructive sleep apnea. *Chest* **133**: 1135–1141.

Kushida CA, Morgenthaler TI, Littner MR *et al* (2006). Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. *Sleep* **29**: 240–243.

Lam B, Sam K, Lam JM, Lai AK, Lam C-L, Ip MM (2011). The efficacy of oral appliances in the treatment of severe obstructive sleep apnea. *Sleep Breath* **15**: 195–201.

Li W, Xiao L, Hu J (2013). The comparison of CPAP and oral appliances in treatment of patients with OSA: a systematic review and meta-analysis. *Respir Care* **58**: 1184–1195.

Lim J, Lasserson TJ, Fleetham J, Wright JJ (2006). Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev* ?????: ????–????. **8**

Lowe AA, Sjoholm TT, Ryan CF, Fleetham JA, Ferguson KA, Remmers JE (2000). Treatment, airway and compliance effects of a titratable oral appliance. *Sleep* **23**(Suppl. 4): S172–S178.

Marin JM, Carrizo SJ, Vicente E, Agusti AG (2005). Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* **365**: 1046–1053.

Marklund M, Stenlund H, Franklin KA (2004). Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest* **125**: 1270–1278.

Menn SJ, Loube DI, Morgan TD, Mitler MM, Berger JS, Erman MK (1996). The mandibular repositioning device: role in the treatment of obstructive sleep apnea. *Sleep* **19**: 794–800.

Neill AM, Whyman R, Bannan S, Jeffrey O, Campbell A (2002). Mandibular advancement splint improves indices of obstructive sleep apnoea and snoring but side effects are common. *N Z Med J* **115**: 289–292.

O'Connor GT, Caffo B, Newman AB *et al* (2009). Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *Am J Respir Crit Care Med* **179**: 1159–1164.

Pancer J, Al-Faifi S, Al-Faifi M, Hoffstein V (1999). Evaluation of variable mandibular advancement appliance for treatment of snoring and sleep apnea. *Chest* **116**: 1511–1518.

Phillips CL, Grunstein RR, Darendeliler MA *et al* (2013). Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea. *Am J Respir Crit Care Med* **187**: 879–887.

Randerath WJ, Heise M, Hinz R, Ruehle KH (2002). An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. *Chest* **122**: 569–575.

Rider EA (1988). Removable Herbst appliance for treatment of obstructive sleep apnea. *J Clin Orthod* **22**: 256–257.

Rose E, Staats R, Schulte-Mönting J, Jonas IE (2002). Treatment of obstructive sleep apnea with the Karwetzky oral appliance. *Eur J Oral Sci* **110**: 99–105.

Schiavoni R (2011). The Herbst appliance updated. *Prog Orthod* **12**: 149–160.

Sullivan CE, Issa FG, Berthon-Jones M, Eves L (1981). Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* **1**: 862–865.

Takahashi K, Chin K, Akamizu T *et al* (2008). Acylated ghrelin level in patients with OSA before and after nasal CPAP treatment. *Respirology* **13**: 810–816.

Thomas JJ, Ren J (2012). Obstructive sleep apnea and cardiovascular complications: perception versus knowledge. *Clin Exp Pharmacol Physiol* **??????**: ??????–??????. **9**

Tsuiki S, Ito E, Isono S *et al* (2013). Oropharyngeal crowding and obesity as predictors of oral appliance treatment response to moderate obstructive sleep apnea. *Chest* **?????**: ?????–?????. **10**

Weaver TE, Grunstein RR (2008). Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* **5**: 173–178.

Won HS, Seo MD, Jung SJ *et al* (2006). Structural determinants for the membrane interaction of novel bioactive undecapeptides derived from gaegurin 5. *J Med Chem* **49**: 4886–4895.

Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V (2005). Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* **353**: 2034–2041.

Young T, Peppard PE, Gottlieb DJ (2002). Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* **165**: 1217–1239.

Zhang P, Liu J, Long S, Xie X, Guo Y (2014). Association between continuous positive airway pressure and changes in serum leptin in patients with obstructive sleep apnoea: a meta-analysis. *Sleep Breath* **?????**: ?????–?????. **11**

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