Table: Summary of studies about the effects from mandibular advancement devices (MADs)

The device designs are classified into monoblock devices and adjustable devices. The monoblock devices were used in a fixed position or were sometimes adjusted with the help of a dental technician. The adjustable devices are subdivided into those with an adjustment mechanism located in the Midline and those with Lateral adjustment mechanisms that may permit mouth opening. Adjustable devices allow continuous titration of mandibular positioning. All studies are reported in chronological order in each section, respectively.

Comparison MAD vs. placebo - Parallel studies					
Author	Design	EBM	Patient population	Results	Comments
Hans et al. 1997 [23]	RCT, parallel study. Non-customised MAD vs. non-advanced MAD. Monoblock devices. 6-8 mm advancement. 2 weeks treatment. Limited sleep study.	2b	18 patients of 24 (20 males) with RDI<30 finished the protocol. Age 52±12 yrs MAD (n=10); non-advanced (n=8) BMI 29±4; 29±6 kg/m^2 ESS 12±4; 13±5	RDI changed from 36±28 to 21±21 with MAD (p≤0.05) and from 37±44 to 47±47 with non-advanced MAD (ns). Increased RDI in 1/10 patients with MAD and in 6/8 with non-advanced device. ESS decreased with MAD only.	Patients with severe OSA used a non-customised device. RDI was insufficiently reduced by MAD, but not at all with non-advanced MAD. RDI may increase with non-advanced MAD.

Blanco et al. 2005 [14]	RCT, parallel study. MAD and non-advanced MAD. Monoblock devices. 75% of maximum mandibular advancement. 3 months treatment. Polysomnography (PSG)	2b	24 patients (20 males) with AHI≥10 and at least two OSA-symptoms were randomised. MAD; non-advanced MAD (n=8); (n=7) Age 56±12; 53±13 yrs BMI 28±4 kg/m^2 in both groups.	AHI changed from 34±15 to 10±12 with MAD ($p<0.01$) and from 24±12 to 12±8 with non-advanced MAD ($p=0.05$). 57% of the patients had a complete response (AHI<5 and the resolution symptoms) with MAD. Effect on daytime sleepiness, snoring and quality of life only from MAD.	Small sample size. Some effect on AHI also from non-advanced device, despite no reduction in either supine or lateral AHI. Positional changes may have influenced the results
Petri et al. 2008 [30]	RCT, parallel study. MAD vs. non-advanced MAD vs. no intervention. Monoblock devices.	1b	81 patients (66 males) out of 93 with AHI of >5 fulfilled the study. Mean age was in between 49-50 yrs,	AHI changed from 39±24 to 25±28 with MAD ($p<0.001$), from 33±22 to 32±25 with non-advanced MAD (ns) and from 34±26	Significant effects on sleep apnoea and daytime sleepiness from MAD compared with placebo. The first study

	Mandible in the most comfortable protrusive position. Adjustment if necessary. 4 weeks study. PSG		BMI 31 kg/m^2 and ESS 11-12 in the randomisation groups.	to 33±25 with “no intervention” (ns). AHI<5 and a resolution in symptoms in 29% of the patients with MAD. ESS decreased and quality of life improved with MAD.	that compares the effects of a non-advanced MAD compared with “no intervention”. No difference in outcome.
Comparison MAD vs. placebo - Cross-over studies					
Author	Design	EBM	Patient population	Results	Comments
Mehta et al. 2001 [28]	RCT, cross-over study. Adjustable MAD (Lateral) vs. control splint in lower jaw. Titration until the resolution of symptoms or maximum comfortable limit. One week with each device.	1b	28 patients with AHI≥10 and ≥2 OSA symptoms were recruited. 24 patients (19 males) finished the protocol. Age 48±9 yrs BMI 29±3 kg/m^2 ESS 10±1	AHI changed from 27±17 (SD) to 14±2 (SEM) with MAD and to 30±2 with control splint. Lower AHI with MAD (p<0.0001). Complete success (AHI<5 and resolution of symptoms) in 38% of the patients and AHI<10 in	Short evaluation time. The study shows a clear effect from MAD compared with a control splint. Better effect in milder, less obese patients. The acclimatisation period may be long for MAD.

	1 week wash-out. Acclimatisation: 20±9 (5-40) (range) weeks. PSG Cephalogram			54%. Snoring frequency was lower with MAD ($p<0.005$). Better effect on sleep apnoea in patients with milder disease, smaller neck circumference, wider pharynx or a backwardly angulated mandible.	
Gotsopoulos et al. 2002 [22]	RCT, cross-over study. Adjustable MAD (Lateral) vs. control splint in upper jaw. Titration until maximum comfortable limit of advancement. 4 weeks with each	1b	73 patients (59 males) of 85 with RDI≥10 and ≥2 OSA symptoms finished the protocol. Age 48±11 yrs BMI 29±5 kg/m^2 ESS 11±5 56% had moderate and 29% had severe OSA.	RDI changed from 27±2 (SEM) to 12±2 with MAD and to 25±2 with control splint ($p<0.0001$ MAD vs. control). Complete success (RDI<5) with MAD was achieved in 36% of the patients. ESS decreased with both	Clear effects on respiratory variables including snoring from MAD compared with control splint. Subjective daytime sleepiness decreased also with control splint. MAD more frequently normalised

	device. 1 week wash-out. Acclimatisation: 8 (2-22) (range) weeks. PSG MSLT			devices. Lower treated value with MAD. MSL was longer with MAD than control. Both subjective and objective snoring frequency and intensity were lower with active device ($p<0.0001$). 99% of the patients desired to continue with MAD and 49% with the control splint. Significantly more patients reported side-effects with active device than with control splint.	ESS. Many patients wanted to continue with the control splint, which highlights the need for objective control of treatment effects.
Johnston et al. 2002 [25]	RCT, cross-over study. Monoblock MAD vs. control device in upper	2b	20 patients (16 males) of 21 with ODI≥10 finished the protocol.	AHI changed from 32±21 to 23±23 with MAD and to 38±25 with control device.	Some effect on sleep apnoea from MAD compared with a control

	jaw. 75% of maximum mandibular advancement. 4-6 weeks with each device. Limited sleep study.		Age 55±7 yrs BMI 32±6 kg/m^2 ESS 14±6 kg/m^2	(p=0.01 MAD vs. control). Treatment success (AHI<10) in 33% of the patients with MAD. One of 6 subjects with pre-treated AHI>50 had success. ESS and reported snoring did not differ between devices.	device in patients with severe OSA. Similar symptomatic outcome from the devices. Poor success rate in the most severely affected OSA patients.
Naismith et al. 2005 [29]	RCT, cross-over study. Adjustable MAD (Lateral) vs. control splint in upper jaw. Titration until maximum comfortable limit of advancement. 4 weeks with each device.	1b	73 patients (59 males) of 86 patients with AHI≥10 and at least two OSA-symptoms completed the protocol. Age 48±11 yrs Mean BMI 28 and 30 kg/m2 in the randomisation groups.	AHI changed from 27±15 to 12±12 with MAD and to 25±15 with control splint. (p<0.01 between devices). 36% of the patients had an AHI<5 and 55% had an AHI<10 with MAD. Improvements in self-reported	Some aspects of neurobehavioral functioning improved with MAD compared with a control splint. Factors which may be as important as sleepiness such as fatigue, tiredness and lack of energy

	1 week wash-out. Acclimatisation: 8±4 weeks. PSG			sleepiness, fatigue/energy levels and vigilance/psychomotor speed from MAD.	improved by MAD.
Comparison MAD vs. placebo or CPAP – Parallel study					
Author	Design	EBM	Patient population	Results	Comments
Aarab et al. 2011 [11]	RCT, parallel study. Adjustable MAD (Midline) vs. CPAP vs. placebo splint in upper jaw. Most effective of 4 mandibular positions. 6 months treatment. PSG	2b	Out of 219 eligible patients, 64 were included and 57 patients finished the protocol. Mean age was 50-55 yrs, mean BMI 27-31 kg/m^2 and mean ESS 10-12 in the randomisation groups.	At baseline, mean AHI was 22, 21 and 20 in the MAD, CPAP and placebo groups, respectively. With MAD these values decreased 16 steps with MAD, 20 with CPAP and 5 with placebo. There was a significant difference between the two active treatments and the placebo intervention	Insignificant difference in AHI-reduction between MAD and CPAP may be explained by small study sample. The p-value was 0.09. Treatment failure was found in some patients who were treated with MAD, but in no patient treated with CPAP. Lower BMI in MAD group might have

				(p<0.001), but not between MAD and CPAP (p=0.09). All interventions reduced AHI. Baseline BMI was lower in the MAD group than the other groups. No difference in symptomatic effects and compliance between the three groups. Best effect of CPAP and poorest effect of placebo on snoring. Side-effects were reported from both MAD and CPAP, but not from placebo.	influenced the results. Placebo effects on symptoms. Best effect on snoring from CPAP.

Comparison MAD vs. placebo or CPAP – Cross-over study					
Author	Design	EBM	Patient population	Results	Comments
Barnes et al. 2004 [13]	RCT, cross-over study. Adjustable MAD (Midline) vs. CPAP vs. placebo tablet. Titration until maximum comfortable limit of advancement. 3 months with each treatment. 2 weeks wash-out. PSG MWT	1b	114 patients with AHI 5-30 were recruited, 80 (63 males) fulfilled the protocol. Age 46±1 (SEM) yrs BMI 31±1 kg/m^2 ESS 10±1	AHI changed from 21±1 (SEM) to 14±1 with MAD ($p<0.001$), to 5±1 with CPAP ($p<0.001$) and to 20±1 with placebo (ns) ($p<0.001$ MAD vs. placebo; $p<0.05$ CPAP vs. MAD). AHI<10 in 49% of the patients with MAD. No difference in ESS between CPAP and MAD. Effects on quality of life and nightly diastolic blood pressure from MAD compared with placebo. No effect on objective	CPAP was the most effective treatment, but produced similar effect on daytime sleepiness and quality of life as MAD. Placebo tablet ineffective on sleep apnoea and daytime sleepiness. Difficulties to estimate effects on neurobehavioral functioning because of placebo effects.

				sleepiness from MAD. Incomplete response on neurobehavioral functioning from both MAD and CPAP. Placebo effects on some measurements. Sleepy and non-sleepy subjects had similar overall treatment responses.	
Comparison MAD vs. CPAP – Parallel studies					
Author	Design	EBM	Patient population	Results	Comments
Lam et al. 2007 [26]	RCT, parallel study. Monoblock MAD and conservative measures (C) (sleep hygiene, weight control) vs. CPAP+C vs. C only.	1b	101 patients (79 males) of 109 with 5≤AHI≤40 (ESS>9 for patients with AHI≤20) fulfilled the protocol. Mean age 45-47 yrs,	AHI changed from 21±2 (SEM) to 11±2 with MAD+C ($p<0.001$), from 24±2 to 3±1 with CPAP+C ($p<0.001$) and from 19±2 to 21±3 with C only	All groups had sleep hygiene and weight control recommendations. CPAP was the most effective treatment. Conservative treatment

	Mandible in the most comfortable protrusive position. 10 weeks treatment. PSG		BMI 27-28 kg/m^2 and ESS 12 in the randomisation groups.	(ns)(p<0.05 CPAP vs. MAD; p<0.001 MAD vs. placebo). All treatments reduced ESS-scores (p<0.05 CPAP vs. MAD). MAD Improved quality of life from MAD and CPAP, but not C. Only CPAP-users reduced weight. No differences in blood pressure effects between the groups.	only, was ineffective on sleep apnoea and weight reduction on a group-level.
Hoekema et al. 2008 [24]	RCT, parallel study. Adjustable MAD (Midline) vs. CPAP. Titration until the resolution of symptoms or maximum	1b	228 patients assessed for eligibility. 103 patients (92 males) with an AHI of ≥5 were randomised. MAD (n=51); CPAP	AHI decreased from 39±31 to 8±14 with MAD and from 40±28 to 2±4 with CPAP (p=0.006 CPAP vs. MAD). Effective treatment (AHI<5 or ≥50%	MAD was less effective than CPAP on sleep apnoea, but had similar symptomatic effects. In terms of success rate, MAD was not considered

	comfortable limit. 8-12 weeks treatment. PSG		(n=52) Age 49±10 yrs for both groups. BMI 32±6; 33±6 kg/m^2 ESS 13±6; 14±6	reduction of AHI to <20 and no symptoms) in 77% of the patients with MAD and in 83% with CPAP. AHI<5 in 57% in all patients, in 84% with mild to moderate OSA and 31% with severe disease. No difference in ESS or quality of life between treatments.	inferior to CPAP in the whole sample. In patients with severe disease CPAP was more effective.
Comparison MAD vs. CPAP – Cross-over studies					
Author	Design	EBM	Patient population	Results	Comments
Ferguson et al.1996 [17]	RCT, cross-over study. Monoblock, non-customised MAD vs. CPAP. 3 mm behind the	1b	27 patients (24 males) with symptomatic OSA, AHI 15-50 were recruited. AHI 25±9	AHI decreased from 20±14 to 10±7 with MAD (p<0.005) and from 18±13 to 4±2 with CPAP (p<0.005). CPAP more	Non-customised MAD was used. Better effect on sleep apnoea and daytime sleepiness from CPAP than from MAD.

	maximum mandibular advancement. 4 months with each device. 2 weeks wash in and 2 weeks wash-out. PSG		Age 46±11 yrs BMI 30±5 kg/m^2 25 patients finished the study.	effective ($p<0.05$). With MAD, 48% received treatment success (AHI<10 and relief of symptoms), 28% had treatment failure and 24% experienced compliance failure. With CPAP, 62% received treatment success and 38% experienced compliance failure. 6 of 7 patients with success from both devices preferred MAD.	Snoring still present with MAD in 6 patients who were treatment or compliance failures. The patients preferred MAD.
Ferguson et al. 1997 [18]	RCT, cross-over study. Adjustable MAD (Midline) vs. CPAP.	1b	24 patients (19 males) with symptomatic OSA, AHI 15-55 were recruited.	AHI decreased from 25±15 to 14±15 with MAD ($p<0.005$) and from 24±17 to 4±2 with CPAP	Customised adjustable MAD was used. Lower AHI with CPAP than with MAD. No difference

	Titration until the resolution of symptoms or maximum comfortable limit. 4 months with each device. 2 weeks wash in and 2 weeks wash-out. PSG		Age 44±11 yrs BMI 32±8 kg/m^2 ESS 11±3 20 patients finished the study.	(p<0.005). Lower AHI with CPAP (p<0.01). Similar decrease in ESS from both devices. With MAD, 55% received treatment success (AHI<10 and relief of symptoms), 40% had treatment failure and 5% experienced compliance failure. Two patients increased their AHI. With CPAP, 70% had treatment success and 30% experienced compliance failure. 7 of 8 patients with success from both treatments preferred MAD.	between devices in symptomatic effects or compliance. Snoring improved in 100% by CPAP and in 55% with MAD. The patients preferred MAD.

Engleman et al. 2002 [16]	RCT, cross-over study. Monoblock MADs vs. CPAP. 80% of maximum comfortable mandibular advancement. 8 weeks with each appliance. Limited sleep study. MWT	1b	51 of 97 consecutive patients with AHI≥5, and ≥2 OSA symptoms including ESS≥8 or sleepiness while driving were recruited. 48 patients (36 males) finished the protocol. Age 46±9 yrs ESS 14±4	AHI decreased from 31±26 to 15±16 with MAD and to 8±6 with CPAP (p=0.001 CPAP vs. MAD). AHI≤5 was found in 19% with MAD and in 34% with CPAP. AHI≤10 was found in 47% with MAD and in 66% with CPAP. Better effect from CPAP on symptoms and quality of life also in milder cases. No difference in objective measurement of sleepiness. Patients who preferred CPAP were heavier.	CPAP more effectively reduced sleep apnoea and symptoms and improved quality of life compared with monoblock MADs in sleepy, mild and more severe OSA patients.

Randerath et al. 2002 [32]	RCT, cross-over study. Adjustable MAD (Lateral) vs. CPAP. About two thirds of maximum mandibular advancement with no further change. PSG during the first night and after 6 weeks with each device. No adjustment of MAD.	1b	20 patients (16 males) with 5≤AHI≤30 were included. Age 57±10 yrs BMI 31±6 kg/m^2	During the first night, AHI decreased from 18 ±8 to 11±8 with MAD ($p<0.05$) and to 4±3 with CPAP ($p<0.01$). No difference in AHI between devices. After 6 weeks, AHI was 14±11 with MAD (ns) and 3±3 with CPAP ($p<0.01$). Lower with CPAP ($p<0.01$). No effect from MAD in any OSA-severity group at 6 weeks. 30% of patients had AHI<10 with MAD. Symptomatic improvement was similar with both devices. Treatment success with	Insignificant effect from MAD-treatment after 6 weeks treatment raises the question whether the effect from MAD may decline. It is possible that more advancement was needed. MAD was easier to use than CPAP. Similar symptomatic improvement from MAD and CPAP indicates a risk that patients continue with a suboptimal treatment.

				MAD was related to a higher weight and lower age.	
Tan et al. 2002 [34]	RCT, cross-over study. Monoblock MAD or adjustable MAD (Lateral) vs. CPAP. 2 months with MAD or CPAP. 75% of maximum comfortable mandibular advancement. Adjustment if necessary. 2 weeks wash-out. PSG	2b	24 patients (20 males) of 46 with 10≤AHI<50 were included. Age 51±10 yrs BMI 32±7 kg/m^2 ESS 13±5 21 patients completed the protocol.	AHI decreased from 22±10 to 8±11 with MAD and to 3±3 with CPAP ($p<0.001$ for both devices). ESS decreased with both treatments ($p<0.001$). No difference in AHI or ESS between devices. Treatment success (AHI<10) with MAD in 67% of the patients and compliance failure in 4%. Treatment success with CPAP in 92% of the patients and	Small study shows similar effects from MAD and CPAP on respiratory variables and daytime sleepiness, although high success rate with CPAP. Patients preferred MAD over CPAP.

				compliance failure in 8%. 17 of 21 (81%) patients preferred MAD.	
Gagnadoux et al. 2009 [19]	RCT, cross-over study. Adjustable MAD (Lateral) vs. CPAP. 2 months with each device after one-night effective titration of both devices. PSG Limited sleep study Osler test	1b	69 patients with AHI 10-60 were recruited, 59 were randomised after successful titration. Age 50±9 yrs BMI 27±4 kg/m^2 ESS=11±5 56 completed the protocol.	AHI changed from 34±13 to 6 (3-14) (median and interquartile range) with MAD and to 2 (1-8) with CPAP. CPAP more effective (p=0.001). Complete response (≥50% reduction and AHI<5) in 73% with CPAP and 43% with MAD. Subjective and objective sleepiness decreased. No difference between devices. Positive and negative predictive values	Both appliances effectively reduced symptoms and AHI, although CPAP was more effective on sleep apnoea. A negative result from the titration procedure was a weak predictor for treatment failure. Self-reported compliance was higher with MAD and the majority of the patients preferred that treatment.

				for success from MAD titration were 85% and 45%, respectively. 70% of the patients preferred MAD.	
Long-term comparison MAD vs. surgery, CPAP or between appliance designs – Parallel studies					
Author	Design	EBM	Patient population	Results	Comments
Walker-Engström et al. 2002 [37]	RCT, parallel study. Monoblock MAD vs. UPPP. Follow-up after 4 yrs. Limited sleep study.	1b	95 patients with 5<AI<25 were included. MAD (n=32); UPPP (n=40) completed the 4-year follow-up. Age 49 (47-52); 51 (49-53) yrs (±95%CI) BMI 27 (26-28) in both groups.	AHI decreased from 18±3 to 5±3 after one year with MAD (p<0.001) and was 7±3 after 4 yrs (p<0.01 vs. one year). AHI had decreased from 20±3 to 10±3 one year after UPPP (p<0.001) and was 14±3 after 4 yrs (p<0.01 vs. one yr). Significantly reduced AHI after 4 yrs, but higher	The first randomised long-term comparison of treatment effects from MADs. Better long-term outcome in patients treated with MAD than in patients who had undergone UPPP. Increased AHI between one and 4 years from both treatments.

				treated value compared with one-year follow-up for both treatments. Long-term AHI higher after UPPP than with MAD.	
Ghazal et al. 2009 [21]	RCT, parallel study. Adjustable devices, MAD (Lateral) vs. MAD (Midline). Titration of mandibular positioning. Follow-up after 6 months and 24 months. PSG	1b	133 patients were assessed. 103 patients with AHI 5-40 were randomised. MAD (Lateral) (n=51); MAD (Midline) (n=52) Age 51±11; 50±11 yrs. BMI 26±3 kg/m^2 in both groups. ESS 8±2; 10±3 45 patients fulfilled the 24 months follow-up.	AHI decreased from 23 (7-32) (median and interquartile range) to 9 (0-16) with MAD (Lateral) and from 21 (7-40) to 5 (0-21) with MAD (Midline) short-term. Better effect from MAD (Midline). Daytime sleepiness and quality of life improved with both appliances. At long-term follow-up, AHI was 5 with both	Both appliances were effective in the short and longer term, although there were smaller differences between them. It is possible that the longer term effectiveness of a device may vary in relation to construction details including comfort for the patients.

				appliances. Snoring and daytime sleepiness increased between the follow-ups. Complete long-term response (AHI<5) in 35% with MAD (Lateral) and 25% with MAD (Midline). Compliance failure in 26% with MAD (Lateral) and 42% with MAD (Midline).	
Aarab et al. 2011 [12]	RCT, parallel study. Adjustable MAD (Midline) vs. CPAP 1 yr. treatment. PSG	2b	21 patients randomised to MAD-treatment and 22 patients to CPAP-treatment from a previous study (Aarab 2010) were followed up.	The reduction in AHI after one year was smaller with MAD than with CPAP ($p<0.0001$). The mean difference was 4. The MAD group had a smaller effect on arousal index	Better effect from CPAP than MAD in the longer term. Similar symptomatic effect. More patients stopped using CPAP because of side-effects, but similar proportion of

			Age 50±9; 55±10 yrs BMI 27±3; 31±3 kg/m^2 ESS=12±6; 11±4 in the MAD-group and CPAP-groups, respectively. 15 MAD-treated patients and 13 CPAP-treated patients finished the study protocol.	($p<0.0001$) than the CPAP group. There was no difference between the two groups in change of EDS. Compliance did not differ between the groups. From study start, 6 patients had discontinued CPAP-treatment and two patients had stopped with MAD-treatment because of side-effects. Another 3 patients had insufficient effect from MAD and were recommended CPAP.	patients had either side-effects or a suboptimal treatment effect from the treatments.

Comparison between MAD designs – parallel studies					
Author	Design	EBM	Patient population	Results	Comments
Tegelberg et al. 2003 [35]	RCT, parallel study. Monoblock MAD with 50% mandibular advancement vs. 75% advancement. One year treatment. Limited sleep study.	1b	74 patients with 5≤AI≤25 started. 50%-MAD; 75%-MAD (n=29); (n=26) completed 5±1; 6±1 mm advancement Age 52 (49-55); 54 (52-56) yrs (95%CI) at baseline BMI 27 (26-28); 28 (27-29) kg/m^2	AHI decreased from 16±3 (95%CI) to 6±4 with 50%-MAD (p<0.001) and from 19±5 to 6±2 with 75%-MAD (p<0.001). No difference between devices. Treatment success (AHI<10 and AI<5) in 79% of the patients with 50%-MAD and in 73% with 75%-MAD (ns).	Similar effect from MADs with 50% compared with 75% mandibular advancement after one year in patients with milder OSA. The authors recommend starting MAD- treatment with 50% advancement in this group of patients.
Walker-Engström et al. 2003 [36]	RCT, parallel study. Monoblock MAD with 50% advancement vs. 75% advancement.	1b	86 men with AI≥20 were included. 50%-MAD; 75%-MAD (n=37); (n=40)	AHI decreased from 47±5 to 17±6 with 50%-MAD and from 50±5 to 16±6 with 75%-MAD (p<0.001	Higher success rate from 75% compared with 50% advancement after 6 months in patients with

	6 months treatment. Limited sleep study.		completed. 5; 7 mm advancement Age 54 (52-56); 50 (48-53) yrs (95%CI) at baseline BMI 31±1; 31±1 kg/m^2 ($^{\pm}$95%CI)	for both devices). No difference between them. Treatment success (AHI<10 and AI<5) in 31% of the patients with 50%-MAD and in 52% with 75%-MAD (p=0.04 between devices). Patients with normalised AHI were slimmer. ESS decreased and no difference between devices.	severe disease, although both advancements reduced the AHI to a similar degree. Comparable symptomatic outcome from the devices.
Comparison between MAD designs – cross-over studies					
Author	Design	EBM	Patient population	Results	Comments
Bloch et al. 2000 [15]	RCT, cross-over study. Monoblock-MAD (M-MAD) vs. adjustable	2b	24 patients (23 males) with OSA symptoms and AHI≥5 or sleep-	AHI decreased from 23±3 (SEM) to 8±2 with M-MAD and to 9±2 with H-MAD	Better symptomatic effect from monoblock device. Patients preferred this

	Herbst-MAD (H-MAD) (Lateral). Adjustment of mandibular positioning with both devices. 1 week with each appliance or without any device. Adaptation time 156±14 days (mean±SEM). PSG		disruptive snoring with arousal index of >20/h. Age 51±2 (SEM) yrs BMI 27±1 kg/m^2 ESS 12±1	($p<0.05$ for each device). Treatment success (AHI<10) in 75% of patients using M-MAD and in 67% with H-MAD (ns). ESS decreased with both devices. Better subjective outcome with M-MAD. 63% of the patients preferred the M-MAD and 4% preferred H-MAD.	device. There might be differences in effectiveness and preferences between appliance designs. The need for elastics in the H-MAD might be a weakness.
Pitsis et al. 2002 [31]	RCT, cross-over study. Adjustable MAD (Lateral) with 4 mm interincisal mouth opening vs. 14 mm. Titration until maximum	2b	23 patients (20 males) of 24 recruited completed the protocol. Age 50±10 yrs BMI 31±5 kg/m^2	AHI decreased from 21±2 (SEM) to 8±1 with 4-mm-MAD ($p<0.001$) and to 10±2 with 14-mm-MAD ($p<0.001$). No difference in AHI, ESS or reported	Two different degrees of mouth openings were tested and there were no differences in respiratory variables or daytime sleepiness between them.

	comfortable limit of advancement. 2 weeks with each device. 1 week wash-out. Acclimatisation with 4-mm-MAD. PSG			snoring between devices. 4-mm-MAD was preferred by 78% of the patients and 14-mm-MAD by 22% ($p<0.007$ between devices).	The patients preferred the device with a smaller mouth opening.
Rose et al. 2002 [33]	RCT, cross-over study. Karwetzky activator (K-MAD) vs. Silencor (S-MAD) (Both Lateral). 75% of maximum mandibular advancement. 6-8 weeks with each device.	2b	26 patients (22 males) with mild OSA were included. Age 57±5 yrs BMI 28±3 kg/m^2 16 patients completed the protocol.	RDI decreased from 16±5 to 6±3 with K-MAD and from 16±4 to 7±5 with S-MAD ($p<0.01$ for each device). Better effect from K-MAD ($p<0.01$). Similar effects on daytime sleepiness and snoring from both appliances. More problems during S-	Better effect on sleep apnoea from Karwetzky activator than Silencor indicates that appliance stability may be of importance for the treatment outcome. Similar symptomatic outcome from both devices.

	Wash-out 2-3 weeks. PSG, limited sleep study.			MAD-treatment in terms of repairs.	
Lawton et al. 2005 [27]	RCT, cross-over study. Herbst-MAD or Twin Block-MAD (Both Lateral). In maximum comfortable limit of advancement and adjusted if necessary. 2 weeks wash-out. Limited sleep study.	2b	49 patients evaluated for eligibility. 16 patients (12 males) completed the protocol. Age 45 (24-68) (range) yrs BMI 29 (24-51) kg/m^2 ESS 10 (2-18)	AHI changed from 46 (29-68) to 25 (0-45) with Herbst-MAD and to 34 (9-63) with Twin Block-MAD. No difference in AHI, ESS, quality of life or side-effects between devices. 56% of the patients preferred Herbst-MAD and 31% preferred Twin Block-MAD.	The patients had severe sleep apnoea and an insufficient treatment response, which makes comparison between devices difficult.
Gauthier et al. 2008 [20]	RCT, cross-over study. Adjustable MADs, Klearway vs. Silencer. Both (Midline).	2b	16 patients (11 males) of 19 fulfilled the protocol. Age 48±2 (SEM) yrs	RDI decreased from 10±1 to 7±1 with Klearway ($p<0.01$) and to 5±1 with Silencer ($p<0.001$)	Minor differences in objective and subjective outcome between the two MAD designs.

	Titrated appliances. 3 months with each device. PSG		BMI 29±1 kg/m^2	(p≤0.05 between appliances). No difference in improvement in symptoms or quality of life or compliance between devices. Klearway was more comfortable.	
Vanderveken et al. 2008 [38]	RCT, cross-over study. Custom-made MAD_{CM} vs. thermoplastic MAD_{TP} Monoblock devices. 65% advancement with MAD_{CM} and 50% with MAD_{TP}. 4 months with each device. 1 month wash-out. PSG	1b	35 patients (29 males) of 38 with AHI≤40 finished at least one arm. Age 49±9 yrs BMI 28±4 kg/m^2 ESS=8±5 23 patients completed the study.	AHI changed from 14±12 to 6±8 with MAD_{CM} (p<0.01) and to 11±9 with MAD_{TP} (ns). Complete success (AHI<5 and reduced snoring) in 49% of the patients with MAD_{CM} and in 17% with MAD_{TP}. Compliance failure in 6% with MAD_{CM} and 31% with MAD_{TP}.	Significant effect on sleep apnoea only from the custom-made device. The prefabricated device could not be recommended as a therapeutic option or as a screening tool.

				Treatment failure in 34% with MAD_{CM} and 37% with MAD_{TP}. 82% of the patients preferred MAD_{CM}. 63% of the patients with MAD_{TP} failure had treatment success with the custom-made device.	
Aarab et al. 2010 [10]	Cross-over study. Adjustable MAD (Midline). Four randomised jaw positions, 0%, 25%, 50% and 75% of maximal protrusion. PSG	2b	17 patients (12 males) of 20 OSA patients finished the protocol. Age 49±9 yrs BMI 27±3 kg/m^2 ESS=12±6	AHI decreased from 22±11 to 6±8 in the most effective jaw position ($p<0.001$). The two most advanced positions were most effective on AHI, but also led to more self-reported side-effects.	The authors recommend starting the titration procedure at 50% advancement in order to reduce the initial side-effects.

RCTs investigating other outcomes of MAD therapy					
Author	Design	EBM	Patient population	Results	Comments
Gotsopoulos et al. 2004 [39]	RCT, cross-over study. Adjustable MAD (Lateral) vs. control splint in upper jaw. 4 weeks with each device. 1 week wash-out. PSG	1b	67 patients (53 males) of 75 with AHI ≥10 and ≥2 OSA symptoms were randomised. AHI 27±15 Age 48±11 yrs BMI 29±5 kg/m^2 61 patients fulfilled the protocol.	AHI was reduced about 50% with MAD compared with the control splint. Significant reduction in 24-hour diastolic blood pressure of 2±1 mmHg (SEM) from MAD compared with the control splint ($p=0.001$), but not in 24-hour systolic blood pressure. Awake systolic and diastolic blood-pressure decreased with 3±1 mmHg ($p<0.01$). No significant difference in blood pressure measured	The authors conclude that oral appliance therapy for obstructive sleep apnoea over 4 weeks results in a reduction in blood pressure, similar to that reported from CPAP.

				asleep.	
Hoekema et al. 2007 [40]	RCT, parallel study. Adjustable MAD (Midline) vs. CPAP. 2-3 months treatment. PSG 25-min simulated driving test at midday.	2b	20 patients (17 males) of 30 with an AHI of >5 completed the protocol. AHI 49±33 Age 49±11yrs BMI 33±6 kg/m^2 16 control subjects (13 males) matched for age.	The total number of lapses of attention during simulated driving was significantly higher in untreated OSA patients compared with controls. The lapses of attention decreased from both MAD and CPAP, with no difference between treatments.	The first study of simulated driving skills during MAD therapy. Improved driving performance from both MAD and CPAP therapy. The result must be interpreted with some caution when generalizing to the actual driving situation.
Hoekema et al. 2007 [41]	RCT, parallel study. Adjustable MAD (Midline) vs. CPAP. 2-3 months treatment. PSG Testosterone	2b	47 of 48 men with an AHI of ≥ 5 completed the study. Age 49±9 yrs BMI 31±4 kg/m^2 ESS 13±6	More signs of sexual dysfunction in men with OSA compared with control subjects. No improvement in subjective reports on sexual	None of the treatments significantly improved male sexual functioning after some months treatment with MAD or CPAP.

	measurement and questionnaires.		48 age-matched control subjects without any sexual problems.	functioning or testosterone levels from either MAD or CPAP.	
Hoekema et al. 2008 [42]	RCT, parallel study. Adjustable MAD (Midline) vs. CPAP. 2-3 months treatment. PSG Echocardiography and measurements of natriuretic peptides.	2b	28 patients (25 males) of 51 with AHI>20 and without cardiovascular disease were included. AHI 52±24 Age 50±10 yrs BMI 33±5 kg/m^2 16 patients completed all parts.	Half of the untreated patients with moderate to severe OSA without cardiovascular disease had left ventricular hypertrophy, left ventricular dilatation or elevated natriuretic peptides. Significant improvement in natriuretic peptides was recorded during MAD- treatment.	Preliminary data in a small sample indicates that cardiac function improves from effective MAD- treatment of patients with moderate to severe OSA.
Trzepizur et al. 2009 [43]	RCT, cross-over study. Adjustable MAD (Lateral) vs. CPAP.	2b	12 of 17 patients with OSA [19]. Untreated samples	AHI decreased from 40 (31-49) to 14 (7-18) with MAD and to 2 (1-8) with	Both appliances improved endothelial reactivity with no difference between

	2 months treatment. PSG Measurement of micro vascular reactivity.		without cardiovascular disease: 9 controls with AHI 6 (4-11), median (interquartile range) 12 patients with AHI 32 (24-51). Median age ranged in between 42 and 56 yrs and BMI was in between 27 and 29.	CPAP ($p<0.05$ for both). Acetylcholine induced vasodilatation was smaller in OSAS patients than in matched controls. The vascular reactivity increased with both treatments ($p<0.05$). No difference between them. The increase correlated with the decrease in nocturnal oxygen desaturations from treatment.	them, despite that treated AHI was higher with MAD. Higher self-reported compliance with MAD. The first randomised study of effects on endothelial reactivity from MAD-treatment.

Clinical trials highlighting particular aspects of MAD therapy such as the mechanism of the device or predictors of success					
Author	Design	EBM	Patient population	Results	Comments
Kato et al. 2000 [52]	Case series. Monoblock MAD with 2-, 4-, and 6-mm advancement. At least one week acclimatisation before trial. Measurements of pharyngeal closing pressure. Oximetry	4	37 of 43 patients with ODI>10 accepted to participate. ODI 26 (11-72) (95%CI) Age 49 (27-67) yrs BMI 29 (23-40) kg/m^2 Pharyngeal closing pressure was evaluated in 6 patients.	Each 2-mm mandibular advancement produced approximately 20% improvement in number and severity of nocturnal desaturations. Advancement of mandibular position produced dose-dependent closing pressure reduction of all pharyngeal segments.	Experimental study showing that the improvement of both nocturnal oxygenation and pharyngeal collapsibility was dose-dependently associated with the degree of mandibular advancement.
Lowe et al. 2000 [54]	Case series. Adjustable MAD (Midline). Compliance monitor.	4	38 patients (36 males) with RDI>15 were included. Age 44 (34-61) (range)	RDI decreased from 33±2 (SEM) to 12±2 with MAD ($p<0.0001$). RDI<15 and a resolution of symptoms in	Objective measurement of compliance is possible for MADs in accordance with what is achievable

			yrs BMI 30 (21-39) kg/m^2 The compliance monitor was tested in 8 subjects.	71% of the patients. The index of agreement was 0.99 between the compliance monitor clock time and patients' reports.	for CPAP.
Liu et al. 2001 [53]	Case series. Adjustable MAD (Midline). PSG Upright cephalogram in the natural head position.	4	47 patients (42 males) with symptomatic OSA. Age 49 (25-80) (range) yrs BMI 30 (22-55) kg/m^2 19 patients completed the study.	AHI decreased from 40±17 to 17±12 with MAD ($p<0.01$). Better treatment response at lower age or BMI or in patients with smaller upper airways. Dental and craniofacial predictors were identified.	Ordinary cephalograms that often are available in dental practice were used together with physiological data to predict treatment success for MAD.
Sanner et al. 2002 [57]	Case series. Adjustable MAD (Lateral). PSG MRI during a Müller	4	15 patients (14 males) with OSA. Age 57±9 yrs BMI 31±6 13 patients fulfilled the	AHI decreased from 20±15 to 7±7 with MAD ($p=0.001$). Treatment success (≥ 50% reduction and AHI<10) in 54% of	The airway patency assessed by MRI during a Müller manoeuvre while wearing MAD might be predictive of treatment

	manoeuvre with and without MAD in supine position.		protocol.	the patients. Five of 7 responders had no significant pharyngeal obstruction during the Müller manoeuvre with MAD, while 4 of 6 non-responders had persistent obstructions.	success with MAD.
Skinner et al. 2002 [58]	Case series. Adjustable MAD (Midline). PSG Cephalogram in supine position. 6 to 8 weeks treatment.	4	14 patients (13 males) of 15 with OSA 10≤AHI≤40 or CPAP-intolerance finished the study. Age 48±11 yrs BMI 29±5 kg/m^2	AHI decreased from 34±22 to 10±5 (p=0.001). The baseline distance between the hyoid bone and the mandibular plane was the only cephalometric variable associated with a successful clinical outcome.	Small study showed that cephalometry had limited value for prediction purposes.

Ng et al. 2003 [3]	Case series. Adjustable MAD (Lateral). After one week wash-out, upper airway closing pressure during sleep, with and without MAD, was assessed. PSG	4	10 patients (9 males) with AHI≥10 and ≥2 OSA symptoms. Age 44±12 yrs BMI 31±6 kg/m^2	AHI decreased from 25±3 (SEM) to 13±5 ($p<0.05$) and upper airway closing pressure decreased in Stage 2 sleep and in slow wave sleep with MAD ($p<0.05$). The reduction in pharyngeal collapsibility was larger in responders.	MAD decreased the upper airway collapsibility during sleep, particularly in responders. Upper airway closing pressure measurements might be useful for prediction purposes.
Fleury et al. 2004 [50]	Case series. Adjustable MAD (Lateral). Titration with oximetry. PSG	4	40 of 44 patients (36 males) with OSA completed the protocol. Age 57±9 yrs BMI 28±4 kg/m^2 ESS 12±4	AHI decreased from 46±21 to 12±14 with MAD ($p<0.001$). 91% of the patients needed increased advancement from initial 80% of maximal protrusion. 64% of the patients had AHI<10 and a resolution	Highlights the importance of the titration procedure, which was performed based on the combined improvement in symptoms and oximetric recordings.

				of symptoms after a mean of 4 advancements.	
Marklund et al. 2004 [55]	Case series. Monoblock MAD. Follow-up after 573±521 days. Limited sleep study.	4	619 of 630 consecutively treated patients (508 males) were followed-up. Age means: 51 yrs in men and 55 yrs in women (p<0.001). 277 patients had sleep apnoea recordings with the device.	AHI was reduced from a mean of 21 (1-74) (range) to 8 (0-72) (p<0.001). 72% of the patients with an AHI of ≥10 before treatment had an AHI of <10 with MAD. Treatment success related to female gender. Men who had supine dependent sleep apnoea or men who did not increase in weight had a better treatment outcome.	Large non-randomised study that identifies predictors of treatment success in a cohort of consecutively treated patients. 76% of the patients used the device after one year.

Kyung et al. 2005 [2]	Case series. Adjustable MAD. CT scan and cephalogram during wakefulness.	4	14 patients (12 males) with AHI>5 and arousal index >20 were included. Age 50±16 yrs BMI 25±3 kg/m^2	AHI decreased from 45±27 to 11±23 with MAD ($p<0.001$). The retropalatal and retroglossal cross-sectional areas increased ($p<0.05$) with MAD. The enlargement of pharynx was greater in the lateral than in the sagittal dimension.	Advancement of the mandible with MAD produces primarily a lateral widening of the upper airway.
Coruzzi et al. 2006 [47]	Case-control study. Monoblock MAD. 3 months treatment. Heart rate, blood pressure and indices of autonomic cardiac regulation.	3b	10 OSA patients (6 males), otherwise healthy. Age 48±10 yrs BMI 27±1 kg/m^2 10 matched controls (5 males).	AHI decreased from 18±1 (SEM) to 4±1 with MAD. Improved cardiac autonomic modulation from MAD- treatment of OSA-subjects. No difference in treated	Improved cardiac automatic modulation from MAD-treatment in milder, otherwise healthy OSA patients may have favourable implications for the prevention of

	Limited sleep study.			values between OSA patients and control subjects.	cardiovascular disease.
Dort et al. 2006 [49]	Case series. Remotely controlled MAD for prediction. PSG	4	33 of 38 patients (36 males) with RDI≥5 fulfilled the protocol. RDI 27±18 Age 45±10 yrs BMI 30±6 kg/m^2	MAD therapy was successful at target mandibular protrusion in 80% of subjects who had a successful test with the remotely controlled MAD and failed in 78% of those who had an unsuccessful test outcome.	The study shows a titration procedure for MADs in accordance with CPAP titration. The method points out a possible prediction method for MADs. This method may also be used to find the optimal mandibular positioning.
Ng et al. 2006 [56]	Case series. Adjustable MAD (Lateral). After one week wash-out, upper airway	4	12 patients (11 males) with AHI≥10 and ≥2 OSA symptoms. Age 51±9 yrs BMI 28±4kg/m^2	AHI decreased from 22±3 (SEM) to 9±2 with MAD (p=0.01). All 4 patients with primary oropharyngeal collapse	The results indicate that primary oropharyngeal collapse predict treatment success with MADs.

	closing pressure and site of collapse during sleep, with and without MAD, was assessed. PSG			had treatment success (AHI<5) with MAD. Only one of the 8 patients with primary velopharyngeal collapse had a successful outcome.	
De Backer et al. 2007 [48]	Case series. Monoblock MAD. PSG Upper airway imaging techniques combined with computational fluid dynamics for prediction.	4	10 OSA patients (8 males) with AHI<40 (1-31) (range). Age: 44-60 yrs BMI: 24-34 kg/m^2	The results indicated that a predicted decrease in upper airway resistance and an increase in upper airway volume correlate with both a clinical and an objective improvement from MAD.	The results suggest that the outcome of MAD-treatment can be predicted using this upper airway modelling technique.
Itzhaki et al. 2007 [51]	Case-control study. Adjustable MAD (Lateral). After 3 months and one	3b	16 sleepy patients (11 males) of 25 with AHI≥10 Age 54±8 yrs	AHI decreased from 30±19 to 18±11 after 3 months and to 20±12 after one year with MAD (p<	Improved endothelial function was found after one year MAD-treatment, although apnoeic events

	year. Markers of oxidative stress and evaluation of endothelial function.		6 untreated OSA patients. Age 43±11 yrs 10 matched controls. Age 50 ±4 yrs BMI: 28 kg/m^2 in all groups.	0.005 for both). Endothelial function and levels of oxidative stress markers improved with MAD. After one year there were no differences compared with reference levels.	were not completely eliminated. A reduction in cardiovascular complications from treatment still needs to be shown.
Zeng et al. 2007 [60]	Case series. Adjustable MAD (Lateral). PSG Spirometry	4	54 patients (40 males) with OSA and at least two symptoms were included. Mean age 51 and 53 yrs and BMI 28 and 31 kg/m^2 in responders and non-responders, respectively.	The results suggest that flow-volume curves, in combination with BMI, age and baseline AHI may have a role in the prediction of treatment response with MAD (>50% reduction in AHI).	A method that may be useful to predict treatment effects from MADs is presented.

Zeng et al. 2008 [61]	Case series. Adjustable MAD (Lateral). PSG Rhinomanometry	4	38 OSA patients (29 males) were eligible for the study. Mean age 51and 55 yrs and BMI 29 and 34 kg/m^2 in the responders and non-responders, respectively.	Baseline nasal airway resistance in sitting position was lower in responders (≥50% reduction in AHI) compared with non-responders.	A method that may become useful to predict treatment effects from MADs is presented.
Chan et al. 2010 [1]	Case series. Adjustable MAD (Midline). PSG MRI	4	69 consecutive patients with AHI≥10 and at least two OSA-symptoms were recruited. Age 51±10 yrs BMI 29±5 kg/m^2	AHI changed from 27±15 to 12±13 with MAD. With MAD, there was an increase in the total airway volume, predominantly because of an increase of the velopharynx with a lateral displacement of the	The study elucidated the mechanism of MAD regarding its influence on the upper airway dimension in good-responders and poor-responders. The upper airway imaging was performed in supine

				parapharyngeal fat pads away from the airway and anterior movement of the tongue base muscles. The increase in upper airway calibre with MAS occurred only in responders.	position during wakefulness. These results might be of help for prediction purposes.
Chan et al. 2010 [45]	Case series. Adjustable MAD (Midline). PSG Nasendoscopy Müller manoeuvre	4	18 responders (AHI-reduction≥50%); 17 non-responders. Age 54±12; 56±10 yrs BMI 29±5; 31±5 kg/m^2	The upper airway collapse visualised by nasendocopy was greater in non-responders than in responders with MAD in situ during a concomitant Müller manoeuvre.	Nasendoscopy may become a useful tool for the prediction of treatment success with MADs.
Tsuiki et al. 2010 [59]	Case series. Monoblock MAD. 2-3 weeks washout.	4	35 patients of 38 who had used CPAP for 6-13 months.	AHI decreased from 36 to 12 (5-26) with MAD ($p<0.001$). Treatment	The study shows an accessible prediction method, since many

	PSG		Age 55 (41-66) yrs median (interquartile range) BMI 26 (24-29) kg/m^2	success (AHI<5 and >50% reduction in AHI) was associated with a lower CPAP-pressure. Patients with CPAP-pressure ≥11 were unlikely to respond to MAD therapy.	patients have tried CPAP before MAD therapy is initiated. More prospective testing is necessary.
Bosshard et al. 2011 [44]	Case series. Adjustable MAD (Midline). PSG Phrenic nerve stimulation.	4	33 consecutive patients (24 males) were recruited. 26 patients completed the study. Age 51±11 yrs BMI 28±4 kg/m^2 ESS 11±5	Complete or partial success was seen in 14/17 subjects with twitch-induced oropharyngeal collapse and in 4/12 patients with velopharyngeal closure. Treatment response was significantly different in subjects with twitch-	This method that is performed during wakefulness has potential for prediction of success with MAD.

				induced oropharyngeal and velopharyngeal collapse (OR 9.5, 95% CI 1.6 to 52.7).	
Chan et al. 2011 [46]	Case series. Adjustable MAD (Lateral). PSG Spirometry	4	35 patients commencing treatment of OA with a custom-made MAD were recruited. Age 52±11yrs BMI 32±11kg/m^2 AHI 30±18	25 patients were responders and 10 patients were non-responders. Response was defined as ≥50% reduction in AHI. A combined cut-off of an inspiratory flow rate at 50% of vital capacity (MIF_{50}) less than 6.0 L/s and a ratio of the expiratory flow rate at 50% of vital capacity to	This prediction method did not have sufficient strength to reliably predict the response to treatment of OSA with MAD. A combination of a functional and structural assessment of the upper airway might be tested for predictions of success with MAD.

				MIF_{50} of greater than 0.7 correctly classified 49% of the patients. It had a sensitivity of 36% and a specificity of 80%.	