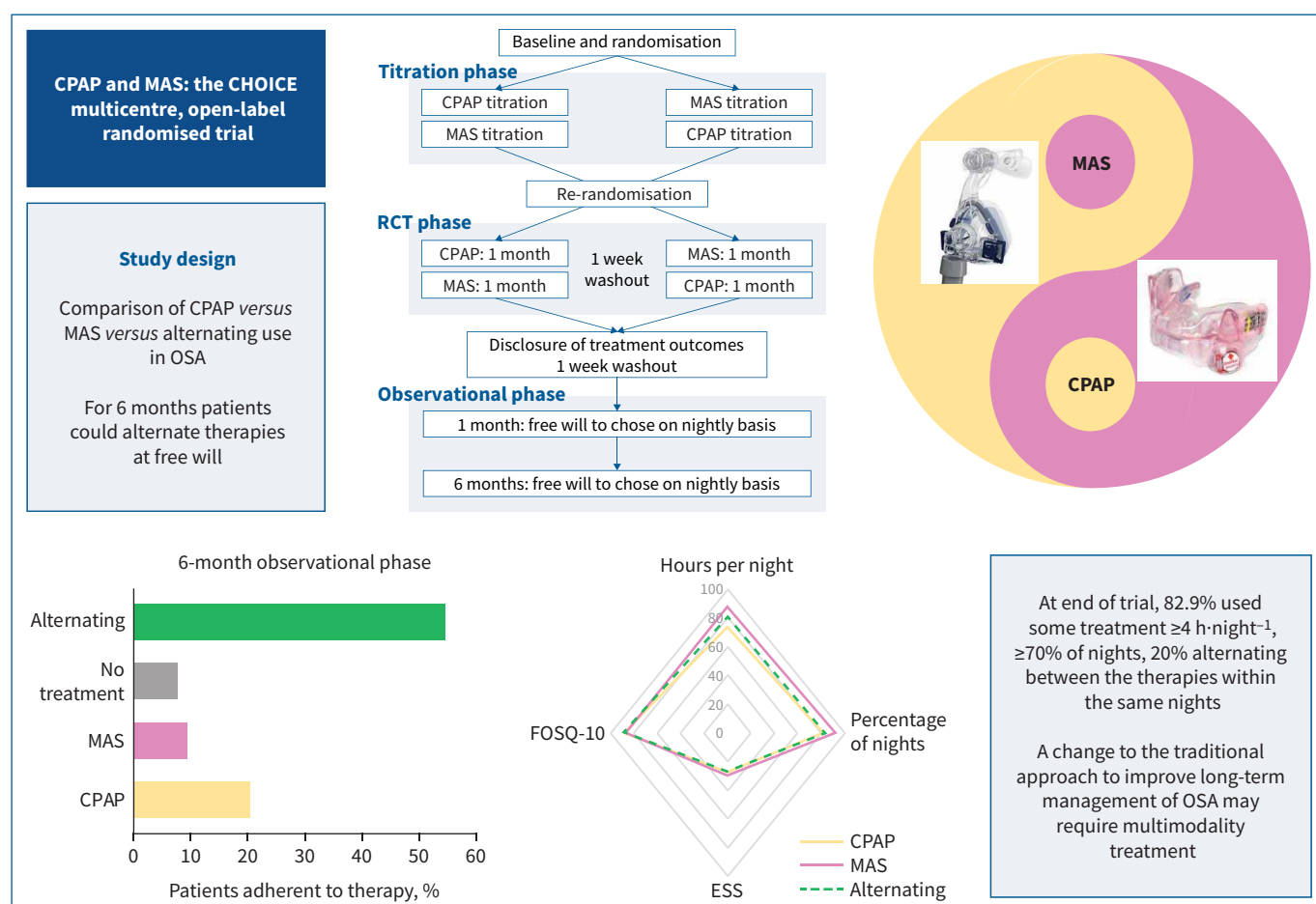


Continuous positive airway pressure and mandibular advancement splints: the CHOICE multicentre, open-label randomised clinical trial

Mona M. Hamoda , Nelly Huynh, Najib T. Ayas, Pierre Rompré, Nick Bansback, Jean-François Masse, Patrick Arcache, Gilles Lavigne, Frederic Series, John A. Fleetham and Fernanda R. Almeida



GRAPHICAL ABSTRACT Overview of the study: the CHOICE multicentre, open-label randomised clinical trial (RCT) on adherence and preference of continuous positive airway pressure (CPAP) *versus* mandibular advancement splints (MAS) in obstructive sleep apnoea (OSA) patients. In the radar plot, all variable are expressed as percentages: 100% values were based on 8 h per night, 30 nights per month, Epworth Sleepiness Scale (ESS) score of 24 and Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10) score of 20.



Continuous positive airway pressure and mandibular advancement splints: the CHOICE multicentre, open-label randomised clinical trial

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Shareable abstract (@ERSpublications)

This RCT confirms higher MAS adherence compared to CPAP, while both demonstrate comparable clinical effectiveness regarding patient-centred outcomes. It highlights that alternating therapy (CPAP–MAS) may have an important role in patient-centred care. <https://bit.ly/492HlpZ>

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Abstract

Background Adherence to continuous positive airway pressure (CPAP) for obstructive sleep apnoea (OSA) continues to be low with high termination rates. Alternative therapies to CPAP are needed. Our objective was to compare objective adherence to CPAP and mandibular advancement splints (MAS) and to evaluate their effectiveness, and additionally to identify treatment usage patterns and the clinical effectiveness of having both therapies.

Methods This multicentre, double-randomised, three-phase trial (titration/crossover/observation) was conducted at three Canadian universities. Eligible participants were treatment-naïve with mild-to-severe OSA. The primary outcome was objectively measured adherence (hours per night) during the crossover phase. Secondary outcomes included efficacy during the crossover phase; adherence during the observational phase; and patient-centred outcomes, blood pressure and side-effects during the crossover and observational phases. Duration of the crossover and observational phase was 2.5 and 6 months, respectively.

Results 81 participants were enrolled in the first randomisation. 79 entered the adaptation/titration phase (mean±SD age 52.3±10.8 years; 58 males), 73 entered the crossover phase (included in the intention-to-treat analysis) and 64 completed the observational phase. Mean objective adherence over 1 month: MAS showed higher adherence than CPAP, 6.0 versus 5.3 h·night⁻¹ (difference 0.7 (95% CI 0.3–1.2) h·night⁻¹; p<0.001). Mean CPAP–MAS difference in efficacy: 10.4 (95% CI 7.8–13.0) events·h⁻¹; p<0.001. During the observational phase 55% (35 out of 64) of participants chose to alternate therapies. All treatments led to substantial improvement in patient-centred outcomes.

Conclusions Despite the higher efficacy of CPAP and higher adherence to MAS, both demonstrate comparable clinical effectiveness on patient-centred outcomes. Having both CPAP and MAS can improve long-term management of OSA.

Introduction

Obstructive sleep apnoea (OSA) is a chronic condition that leads to sleep fragmentation and oxygen desaturation with associated neurocognitive [1] and cardiovascular consequences [2]. There are currently a variety of treatments available for OSA with variable invasiveness, efficacy, effectiveness, patient acceptance and adherence. Based on three large relatively recent trials [3–5], the main obstacle for the effectiveness of OSA treatment is poor CPAP adherence [6] with a 50% termination rate following 3 years



of use [7]. Mandibular advancement splints (MAS) are an alternative to CPAP that have shown high effectiveness, patient acceptance and adherence [8–10]. It is important to individualise the treatment of OSA and tailor it to patient needs, yet there are few studies on the role of alternating therapy in OSA and its impact on adherence to treatment and patient-centred outcomes.

The primary objective of this randomised crossover trial was to compare objectively measured adherence between CPAP and MAS. Secondary objectives were to investigate usage patterns when participants had both available, and to compare outcomes of having both CPAP and MAS monotherapies. Some of the results of this study have been previously reported in the form of an abstract [11].

Methods

Study design

This multicentre, double-randomised, open-label, two-treatment, three-phase clinical study consisted of a titration/adaptation phase, a crossover phase and an observational phase (figure 1 and supplementary material).

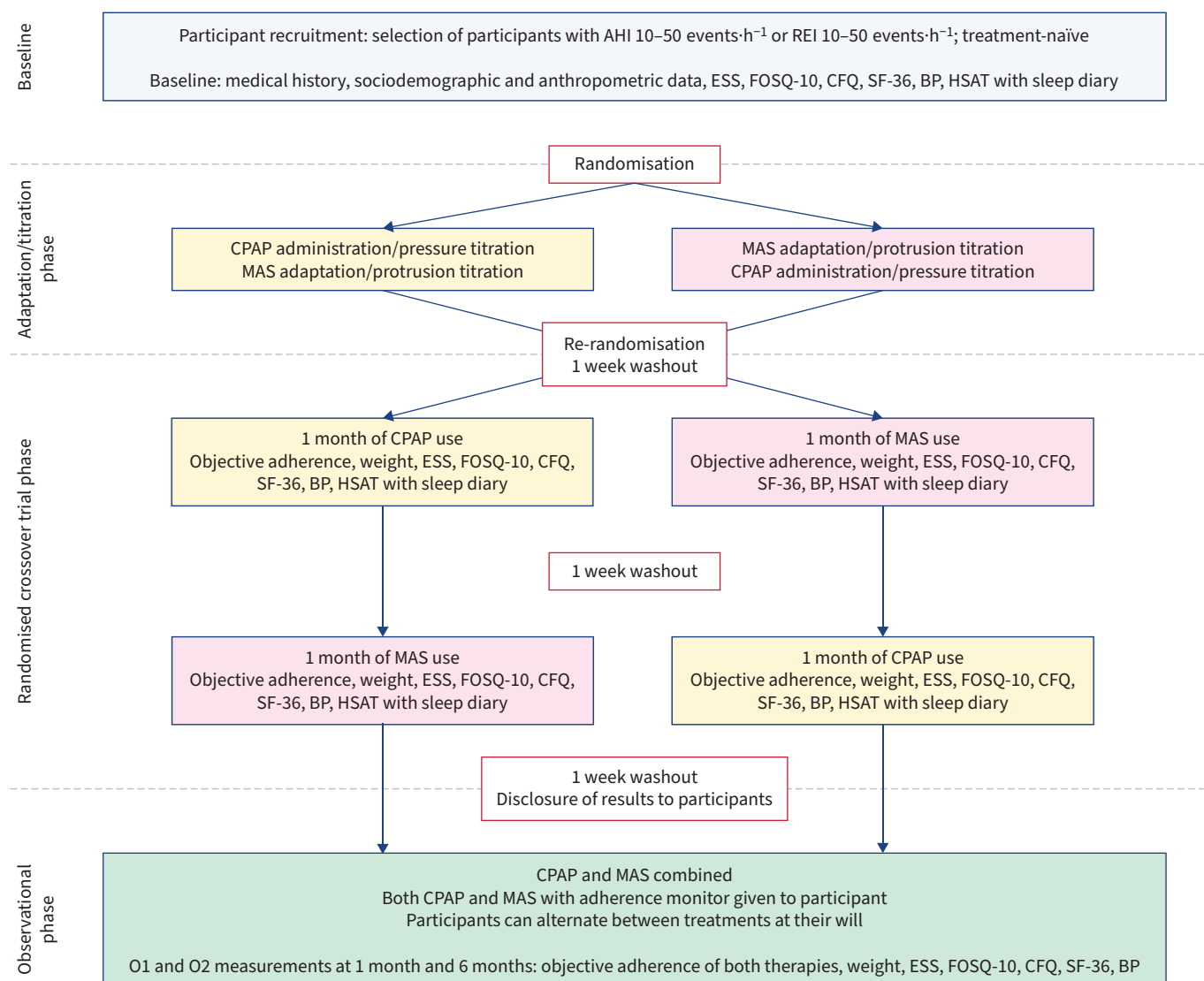


FIGURE 1 Study protocol. AHI: apnoea–hypopnoea index; REI: respiratory event index; ESS: Epworth Sleepiness Scale; FOSQ-10: Functional Outcomes of Sleep Questionnaire-10; CFQ: Chalder Fatigue Questionnaire; SF-36: 36-item Short-Form Health Survey; BP: blood pressure; HSAT: home sleep apnoea test; CPAP: continuous positive airway pressure; MAS: mandibular advancement splints; O1: observation visit 1; O2: observation visit 2.

Study sites and patient population

The CHOICE study (ClinicalTrials.gov: NCT02242617) was conducted at three centres across Canada and approved by the institutional ethics board of each centre: University of British Columbia (H14-01215), Université de Montréal (14-125-CERES-D(2)) and Université Laval (2015-2434). Participants were recruited from hospital-based sleep clinics, age 19–75 years, treatment-naïve (never used CPAP or MAS, nor had surgery for sleep apnoea), overall CPAP and MAS candidates (assessed by sleep physician), and with an objective diagnosis of OSA (apnoea–hypopnoea index (AHI) 10–50 events·h⁻¹, or respiratory event index (REI) 10–50 events·h⁻¹ documented with a Level III portable sleep test (home sleep apnoea test (HSAT)), or an oxygen desaturation index (ODI) ≥10 events·h⁻¹ with the objective diagnosis of OSA performed ≤2 years before recruitment). While the recruitment of mild-to-severe OSA patients was the predetermined objective, inclusion of patients diagnosed by means of a HSAT was added in September 2015 due to Canadian diagnosis protocols (prior to the start of enrolment). Inclusion criteria also included body mass index (BMI) ≤35 kg·m⁻² and the presence of a minimum of eight teeth per arch intra-orally (details of eligibility criteria are provided in the supplementary material). The age range was changed from 30–65 to 19–75 years in June 2016 to be inclusive of a greater population of adults with OSA.

Randomisation and blinding

Participants were randomised twice: 1) to the order of treatment adaptation/titration and 2) to the order of treatment during the crossover phase. Blinding of the participants and study personnel was not possible. Blinding of the statistician was not possible due to his prior familiarity with the study timeline and his generation of the random allocation sequence; however, the technologist scoring the sleep studies was blinded to treatment allocation and the study timeline.

Interventions

CPAP was delivered via a DreamStation AutoCPAP (Philips, Amsterdam, Netherlands) with built-in adherence monitoring. The MAS was a custom-made titratable bibloc (SomnoDent Flex G2; SomnoMed, Crows Nest, Australia) with an embedded accurate and reliable adherence monitoring smartchip (DentiTrac; Braebon Medical Corporation, Kanata, ON, Canada) [12, 13]. We obtained the raw adherence data from each device in the form of hours of nightly use for every night for every participant in the study and used that to generate the calculations.

Procedures

In total, 15 visits were required to complete this study over a period of 1.2–1.5 years for each participant (the greatest variable was titration of treatments). Duration of the crossover and observational phase was 2.5 and 6 months, respectively. During titration and crossover, participants were only given the intervention that they were randomised to. At the end of the crossover phase and following a 1-week washout, a written report was given to participants (disclosure of results) which included their respiratory events data, adherence and questionnaire (Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10)) data with an explanation (full letter example in the supplementary material). During the observational phase, participants had both treatments and were given the freedom to use the treatment of their choice or no treatment, as described in their disclosure letter: “You now have the option to use whatever treatment you prefer on a daily basis”.

Outcomes

The primary outcome was objectively measured adherence (hours per night) assessed at the end of 1 month on each treatment during the crossover phase. Secondary outcomes were adherence during the observational phase (calculated as the combined adherence to both therapies) and HSAT (Alice NightOne; Respironics, Murrysville, PA, USA) at baseline and after 1 month CPAP and MAS (crossover). Secondary outcomes also included ESS [14], FOSQ-10 [15], Chalder Fatigue Scale (CFQ) [16], 36-item Short-Form Health Survey (SF-36) [17], both physical (physical component summary (PCS)) and mental (mental component summary (MCS)) health scores, and side-effects questionnaires [18, 19] assessed at the five main time-points. In-office blood pressure (BP), two-measurement average (automated Omron HEM-780; Omron Healthcare, Kyoto, Japan), was collected and participants were classified as normotensive, stage 1 or stage 2 hypertensive [20]. Although in-office BP was collected as a routine procedure at the five main time-points, it was not one of the main outcomes of the trial.

Statistical analysis

Sample size calculation was based on detecting an average difference of 1 h of adherence between the two treatments with a type 1 error of 0.05 (two-sided), 85% power and standard deviation of 2.0 [8]. Assuming 25% of participants were not going to proceed after the titration phase and anticipating a 15% dropout rate during the crossover phase [8], we needed to recruit 42 participants for the crossover phase. Based on the

recruitment ratio with one-third of those recruited being severe OSA, recruitment was increased to 60 at the beginning of the trial and required another increase to 75 then 80 participants during the trial to enrich our study with severe OSA patients.

Intention-to-treat analysis for the crossover phase was performed for the primary outcome (adherence) and for the respiratory parameters, and included all study participants who underwent the second randomisation. Per-protocol analysis was conducted for all outcomes and included participants who had 1-month CPAP and/or MAS data during the crossover phase. Mixed models were used to estimate treatment effect (details and missing data analysis are described in the supplementary material). Data were analysed using SAS version 9.4 (SAS Institute, Cary, NC, USA) or SPSS version 28 (IBM, Armonk, NY, USA).

Results

Enrolment, attrition and participant characteristics

Enrolment took place between 19 November 2015 and 5 September 2017 (dates that the first and last participants were randomised at their first randomisation). In total, 81 participants were enrolled and included in the first randomisation; one participant dropped out and one was withdrawn before starting the titration/adaptation phase. Of the remaining 79 participants, one participant did not complete the baseline sleep study due to cancer diagnosis. As per protocol, the participant was included as all her other baseline data were available (table 1 and figure 2). 44 participants were included based on a Level I sleep study (mean $\pm$ SD AHI 32.0 $\pm$ 14.7 events $\cdot$ h $^{-1}$; range 11–71 events $\cdot$ h $^{-1}$), 34 had a Level III sleep study (mean $\pm$ SD REI 32.4 $\pm$ 13.7 events $\cdot$ h $^{-1}$; range 11–59 events $\cdot$ h $^{-1}$) and one had a Level IV sleep study (ODI 32.8 events $\cdot$ h $^{-1}$). Five, 39 and 35 participants had mild, moderate and severe OSA, respectively, based on their referral diagnostic sleep study. A new baseline sleep study was conducted with standardised HSAT sleep monitors.

79 participants were included in the titration/adaptation phase (table 1). 73 participants completed the second randomisation (see figure 2 for reasons for withdrawal/dropout) and were included in the intention-to-treat population. All participants adhered to their randomisation groups during the titration and crossover phases. Overall, 64 participants completed all three phases of the study and were included in the analyses of the observational phase (data from the 1-month observation period are also included in the 6-month observation data).

Primary adherence outcome measures

For the primary outcome, average adherence per night over 1 month, MAS showed higher adherence than CPAP: 6.0 versus 5.3 h $\cdot$ night $^{-1}$ (difference 0.7 (95% CI 0.3–1.2) h $\cdot$ night $^{-1}$; $p < 0.001$). CPAP had slightly greater usage (percentage of nights per week) but less nights achieved usage > 4 h. Mean MAS–CPAP difference (for hours per night of treatment use on the nights treatment was used) was 1.1 (95% CI 0.8–1.5) h $\cdot$ night $^{-1}$. High levels of overall adherence to treatment (regardless of which) was noted during the observational phase and the mean $\pm$ SD treatment usage during the 6-month observational phase was 5.3 $\pm$ 2.3 h $\cdot$ night $^{-1}$ over the total duration and 6.3 $\pm$ 1.6 h $\cdot$ night $^{-1}$ when used (tables 2 and 3 and figure 3).

During the 6-month observational phase, 13 (20.3%) participants who completed the trial were highly adherent to CPAP only, six (9.4%) to MAS only, five (7.8%) were considered partially adherent to CPAP or MAS only, five (7.8%) were considered non-adherent to any treatment and the majority 35 (54.7%) chose to use both treatments (figure 4). Of those who alternated between the two treatments, 29 out of 35 (82.9%) were able to reach or exceed treatment adherence criteria of ≥ 4 h $\cdot$ night $^{-1}$ on $\geq 70\%$ of nights. Six (17%) of those alternating were alternating between therapies within the same nights and the rest used both in alternated nights. For the 83% who alternated between nights, the majority did not follow a specific pattern.

Treatment efficacy

The improvement in REI and ODI from baseline to post-treatment was statistically significantly higher in the CPAP group than the MAS group (REI 10.4 (95% CI 7.8–13.0) events $\cdot$ h $^{-1}$ and ODI 9.8 (95% CI 7.3–12.2) events $\cdot$ h $^{-1}$ per intention-to-treat analysis) (table 4). A subgroup analysis of the moderate and severe OSA groups showed that CPAP was able to reduce the REI to a mean of < 5 events $\cdot$ h $^{-1}$ in both groups, while MAS was able to reduce moderate OSA to mild OSA and severe OSA to moderate OSA (table 5).

Patient-centred outcomes (questionnaire scores)

A significant reduction in daytime sleepiness (ESS score) was demonstrated at all time-points relative to baseline ($p < 0.0001$), with no statistically significant differences between treatment time-points (table 6 and supplementary table E2). However, mean difference was greatest between 6-month observation and baseline (3.9 (95% CI 2.1–5.7)). 47% of study participants were considered excessively sleepy (ESS > 10) pre-treatment. There was a significant reduction in ESS scores ($p < 0.0001$) at all time-points in the excessively sleepy subset relative to baseline.

TABLE 1 Baseline characteristics of the study population (n=79)

Age, years	52.3±10.8
Sex	
Male	58
Female	21
Baseline OSA severity	
REI, events·h ⁻¹ (n=78)	21.1±14.5
ODI, events·h ⁻¹ (n=78)	20.2±13.7
BMI, kg·m⁻²	28.5±3.8
BMI categories	
Normal (18.5–<25 kg·m ⁻²)	14
Overweight (25–<30 kg·m ⁻²)	36
Obese (≥30 kg·m ⁻²)	29
Neck circumference, cm	39.5±12.3
Mean office systolic BP, mmHg	128.5±21.1
Mean office diastolic BP, mmHg	83.8±14.0
ESS score	10±5.7
High ESS score [#] (n=33)	15±3.6
FOSQ-10 score	15.4±2.9
Low FOSQ-10 score [¶] (n=64)	14.5±2.5
CFQ score	17.0±5.8
High CFQ score ⁺ (n=33)	22.0±3.8
SF-36	
MCS score	45.2±10.7
Low MCS score [§] (n=18)	29.8±4.6
PCS score	50.3±6.6
Bed partner	48
Snorer (n=76)	72
Comorbidities	
Systemic hypertension	21
Cardiovascular disease	8
Diabetes mellitus	6
Educational level	
High school	10
Higher education	69
Ethnicity	
Caucasian	59
Asian	8
Middle Eastern	4
Hispanic	4
Black	4
Occupational status	
Employed	60
Retired	12
Sick leave	3
Other	4

Data are presented as mean±SD or n. OSA: obstructive sleep apnoea; REI: respiratory event index; ODI: oxygen desaturation index; BMI: body mass index; BP: blood pressure; ESS: Epworth Sleepiness Scale; FOSQ-10: Functional Outcomes of Sleep Questionnaire-10; CFQ: Chalder Fatigue Questionnaire; SF-36: 36-item Short-Form Health Survey; MCS: mental component summary; PCS: physical component summary. [#]: ESS score >10; [¶]: FOSQ-10 score <17.9; ⁺: CFQ score >17; [§]: MCS score <36.

FOSQ-10, CFQ and MCS scores (SF-36) followed a similar trend to ESS scores with statistically significant differences between all treatment time-points and baseline. FOSQ-10 scores improved with a decrease of 2.2 (CPAP), 1.8 (MAS), 2.3 (1 month) and 2.5 (6 months). CFQ scores improved by 6.0 (CPAP), 5.7 (MAS), 6.3 (1 month) and 6.5 (6 months). MCS scores (SF-36) showed a decrease/improvement in quality of life of 4.1 (CPAP), 3.2 (MAS), 4.7 (1 month) and 5.4 (6 months).

There were no significant differences between the treatment time-points. Similarly, the improvement in these scores was greatest for the subset of the study population who were considered highly symptomatic at baseline (table 6). PCS scores (SF-36) did not follow the same trend. There was a statistically significant increase (improvement) in PCS scores only for the 1-month MAS and observation (mean difference 2.4

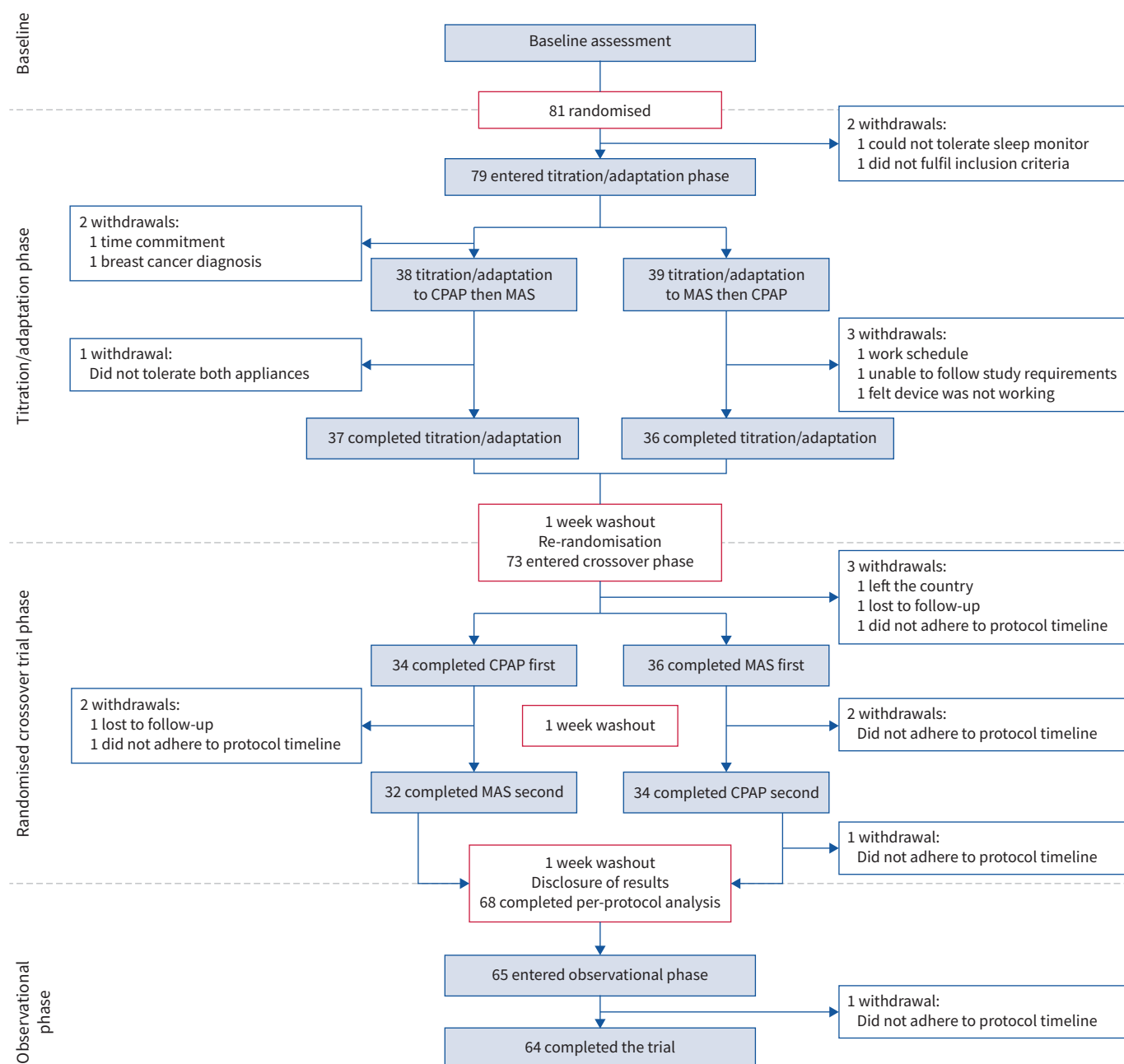


FIGURE 2 Study flowchart. Titration/adaptation phase: participants were optimally titrated to both continuous positive airway pressure (CPAP) and mandibular advancement splints (MAS). Between 4 and 8 months was required to complete this phase. Crossover phase: participants were on CPAP and MAS for 1 month each preceded by a 1-week washout period. A second 1-week washout took place prior to switching to the second treatment device. Observational phase: duration 6 months preceded by a 1-week washout period. Treatment usage was patient led during this phase. Participants had the choice to use one treatment, both or none during this phase.

(95% CI 0.4–4.5) and 3.3 (95% CI 0.4–6.2), respectively) (table 6 and supplementary table E2). An effect of time since initiation of treatment was noted on FOSQ-10 scores and MCS scores (SF-36) during the crossover phase.

Blood pressure

A significant reduction in both systolic BP and diastolic BP was noted for the total sample at some time-points compared to baseline. Furthermore, 74% of participants had stage 1 or 2 systemic hypertension at the beginning of the study. In this hypertensive subset, significant reductions in both systolic BP and diastolic BP were observed at most time-points compared to baseline (supplementary figure E2 and

TABLE 2 Intention-to-treat analysis for objectively measured adherence during the crossover phase of the trial (n=73)

	Crossover phase		Mean MAS—CPAP difference (95% CI)	p-value
	CPAP	MAS		
Number of hours				
Mean hours used (when used [#]), n	5.9±1.6	7.0±1.1	1.1 (0.8–1.5)	<0.0001
Mean hours used (total duration [¶]), n	5.3±2.0	6.0±2.0	0.7 (0.3–1.2)	0.0002
Number of nights				
Nights per week with treatment usage, %	86.7±19.9	80.9±22.2	−5.8 (−11.3– −0.3)	0.0056
Percentage of nights and number of hours				
Nights with usage >4 h (when used [#]), %	81.8±25.4	89.0±17.8	7.2 (0.5–13.8)	0.0062
Nights with usage >4 h (total duration [¶]), %	73.4±30.0	77.0±25.6	3.6 (−3.2–10.3)	0.71

Data are presented as mean±SD, unless otherwise stated. CPAP: continuous positive airway pressure; MAS: mandibular advancement splints. [#]: “when used” represents the number of hours treatment was used divided by the number of nights treatment was used and excludes the nights when treatment was not used; [¶]: “total duration” represents the hours of use divided by the number of nights treatment should have been used as per the study protocol, regardless of if treatment had been actually used or not. For p-values: non-parametric ANOVA-type statistic for repeated measures with treatment, sequence and visit type as fixed effects and participant as a random effect. For difference (95% CI): mixed model for repeated measures with treatment, sequence and visit type as fixed effects and participant as a random effect. Statistically significant p-values following correction for multiple comparisons are in bold.

supplementary table E2). BMI was assessed as a possible confounder for BP changes and showed no difference between all time-points (supplementary table E2).

Side-effects

No serious adverse events were noted throughout the trial, and side-effects showed a reduction in frequency and intensity with time. The main CPAP side-effects included mask leaks and feeling uncomfortable, and the main MAS side-effects included difficulty chewing and discomfort or pain in the teeth and jaws (details in the supplementary material).

Discussion

To the best of our knowledge, this is the first randomised crossover trial comparing CPAP and MAS that is followed by an observational phase assessing the interchangeable use of CPAP and MAS (as per patient

TABLE 3 Per-protocol analysis for objectively measured adherence at the different time-points

	Crossover phase (n=68)		Observational phase (n=64)		p-value ^{a,b,c,d,e}
	CPAP	MAS	1-month observation	6-month observation	
Number of hours					
Mean hours used (when used [#]), n	5.9±1.6	7.0±1.2	6.2±2.1	6.3±1.6	<0.0001, 0.0003, 0.02, 0.002, <0.0001
Mean hours used (total duration [¶]), n	5.3±2.1	6.0±2.1	5.7±2.4	5.3±2.3	0.0008, 0.006, 0.90, 0.27, 0.001
Number of nights					
Mean nights per week with treatment usage, n	6.1±1.4	5.8±1.6	5.9±1.8	5.5±2.0	0.07, 0.21, <0.0001, 0.39, 0.03
Percentage of nights per week with treatment usage, %	87.2±20.6	83.2±23.6	83.7±26.2	78.8±27.6	0.06, 0.23, <0.0001, 0.36, 0.02
Percentage of nights and number of hours					
Nights with usage >4 h (when used [#]), %	81.9±26.3	92.0±17.9	83.4±27.9	84.8±20.9	0.0001, 0.11, 0.29, 0.03, <0.0001
Nights with usage >4 h (total duration [¶]), %	74.2±31.0	78.8±27.7	74.7±32.0	70.5±30.4	0.45, 0.62, 0.05, 0.76, 0.003

Data are presented as mean±SD, unless otherwise stated. CPAP: continuous positive airway pressure; MAS: mandibular advancement splints. [#]: “when used” represents the number of hours treatment was used divided by the number of nights treatment was used and excludes the nights when treatment was not used; [¶]: “total duration” represents the hours of use divided by the number of nights treatment should have been used as per the study protocol, regardless of if treatment had been actually used or not. Non-parametric ANOVA-type statistic for repeated measures with visit type as a fixed effect and participant as a random effect. Statistically significant p-values following correction for multiple comparisons are in bold. ^a: CPAP versus MAS; ^b: CPAP versus 1-month observation; ^c: CPAP versus 6-month observation; ^d: MAS versus 1-month observation; ^e: MAS versus 6-month observation.

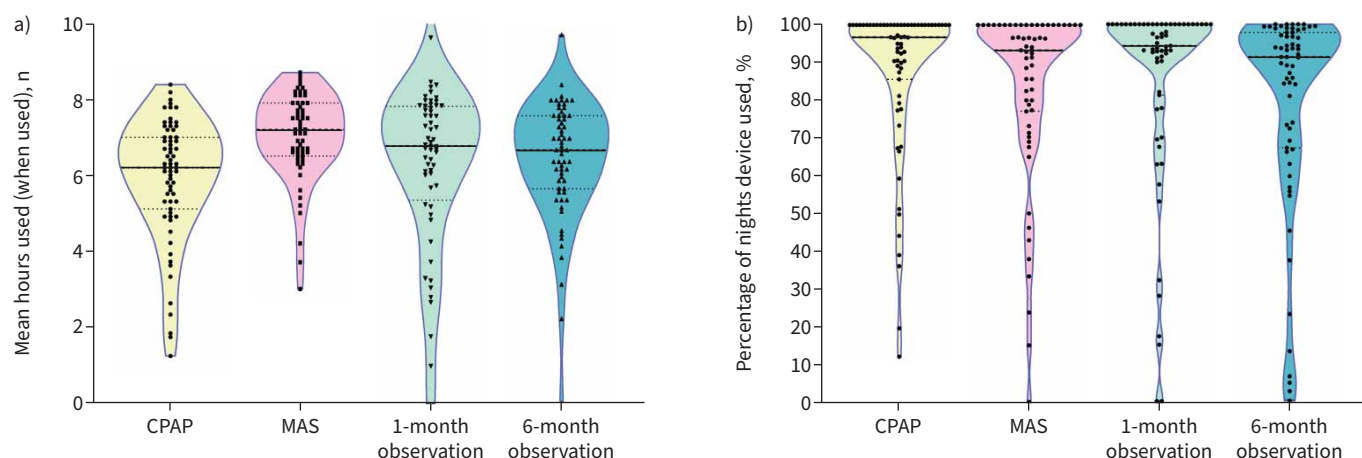


FIGURE 3 Adherence pattern at the different time-points. **a)** Mean number of hours treatment was used (when used) during the 1-month continuous positive airway pressure (CPAP), 1-month mandibular advancement splints (MAS), 1-month observation and 6-month observation periods. **b)** Percentage of nights treatment was used during the 1-month CPAP, 1-month MAS, 1-month observation and 6-month observation periods. Violin plots represent the distribution of the data. Medians and interquartile ranges are indicated. Each dot represents data from a single participant.

choice) over a period of 6 months, while objectively measuring adherence to both treatments throughout the entire study. During the crossover phase, adherence to MAS was significantly higher than to CPAP by a mean of $0.7 \text{ h} \cdot \text{night}^{-1}$ (over 1 month) and $1.1 \text{ h} \cdot \text{night}^{-1}$ (when used). During the observational phase of patient-led OSA therapy, where patients were given the freedom to choose the treatment of their preference, the majority of participants (55%) opted for the use of both therapies and 83% of the participants who alternated between the two therapies were considered highly adherent to treatment ($\geq 4 \text{ h} \cdot \text{night}^{-1}$ on $\geq 70\%$ of nights). Additionally, this led to similar improvements in patient-centred outcomes during the 6-month observation period compared to the time when participants were exclusively on CPAP or MAS monotherapy during the crossover phase. Improvements were more profound in highly symptomatic and hypertensive patients.

It has been previously shown that adherence to CPAP and MAS can be variable and decline with time [21, 22]. A systematic review of studies assessing CPAP adherence over a 20-year time frame showed that short-term adherence (< 6 months) was $4.5 \text{ h} \cdot \text{night}^{-1}$ with a termination rate of 35.5% and long-term adherence (> 6 months) was $4.6 \text{ h} \cdot \text{night}^{-1}$ with a termination rate of 34.2% [23]. Our results show that despite this expected decline, adherence to therapy remained high during the observational phase, which makes our study underpowered for adherence difference. This was surprising and new studies allowing choices of treatment with larger samples are required. Treatment was used for most nights during the observational phase and for a long number of hours during these nights (mean $6.3 \text{ h} \cdot \text{night}^{-1}$), achieved due to participants' ability to use CPAP and MAS interchangeably. Conversely, during the 1 month of CPAP (monotherapy), despite CPAP being used for the majority of nights (87%), participants were unable to use it for extended hours and a $0.5 \text{ h} \cdot \text{night}^{-1}$ increase in adherence leads to a clinically significant difference [24, 25].

OSA is known to be an independent risk factor for systemic hypertension and cardiovascular disease [26, 27], therefore the relevance of BP in OSA management should not be underestimated. Reports indicate adherence to CPAP is often around 42% [3, 4]; nonetheless, 85.7% of our trial participants were able to use OSA therapy for $\geq 4 \text{ h} \cdot \text{night}^{-1}$ on $\geq 70\%$ of nights during the 6-month observational phase. Thus, the increase in overall treatment adherence, regardless of to which treatment, may lead to better treatment outcomes. Our findings show a significant reduction in both systolic BP and diastolic BP during the 6-month observational phase relative to baseline, which suggests that higher adherence results in greater BP reduction. These findings were based on standardised office measurements [20]; new studies with 24-h measurement are required to confirm these findings. At baseline, 19 out of 21 hypertensive patients disclosed taking medication for systemic hypertension, and their medication was not changed during the course of the study. Similar to the findings of PAMIDI *et al.* [28], the high level of adherence to both treatments and the decrease in the number of days with no treatment may have led to greater improvements in systolic BP and diastolic BP, and are in alignment with the work of BRATTON *et al.* [29].

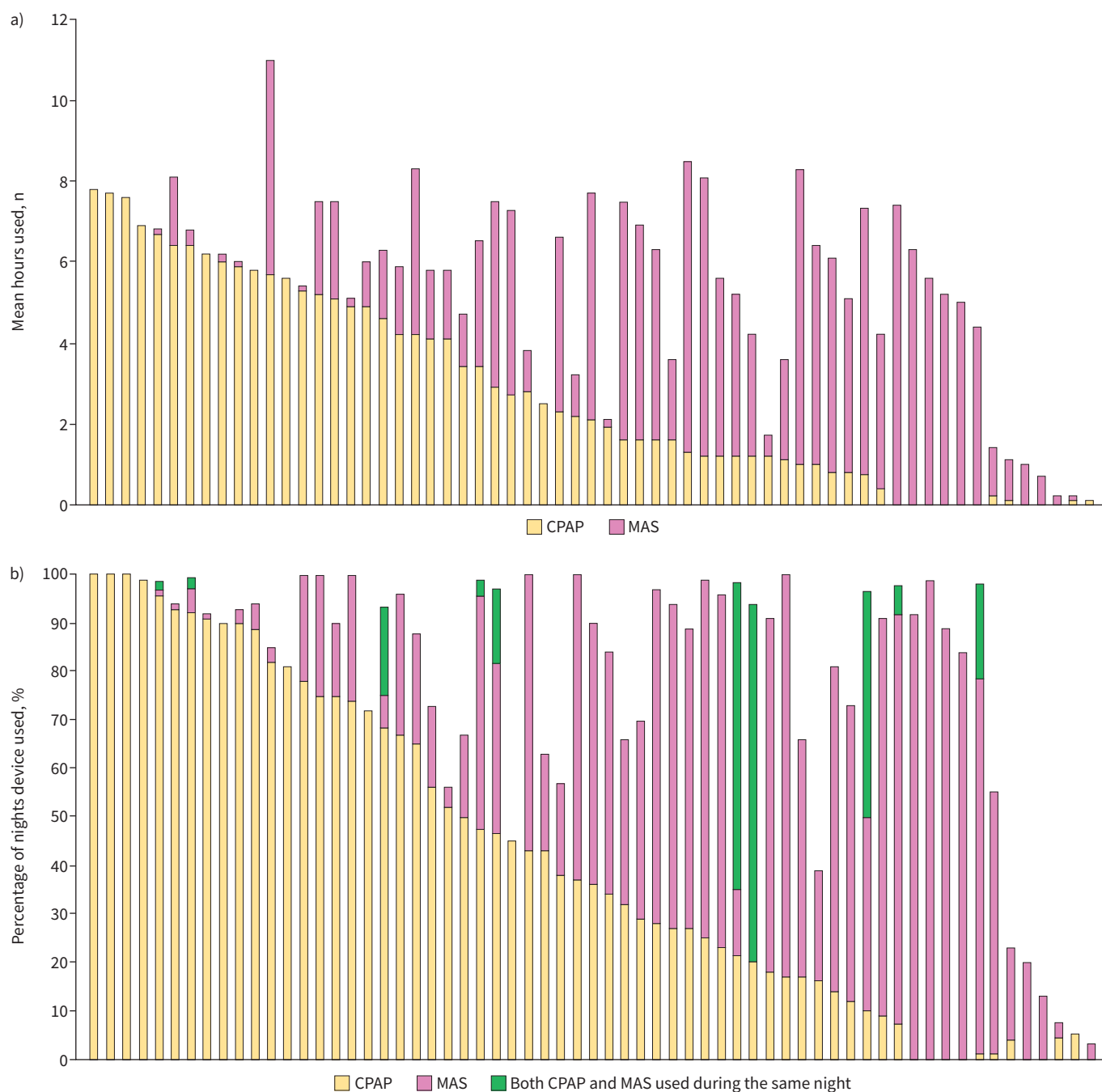


FIGURE 4 All participant's individual objective adherence data for the 6-month observational phase (following the crossover phase). **a)** Mean number of hours of treatment use per night. **b)** Percentage of nights of treatment use. CPAP: continuous positive airway pressure; MAS: mandibular advancement splints.

The results of this trial show a substantial, clinically significant improvement in the severity of symptoms relative to baseline. Our findings are in line with meta-analyses that demonstrate that MAS is comparable to CPAP in reducing symptoms such as sleepiness and snoring, improving quality of life, and reducing BP [8, 29, 30]. Congruent with the findings of STRADLING and DAVIES [31] that showed a positive relation between improvement in outcomes (*i.e.* fatigue and daily functioning) and duration of CPAP use, our findings show that a similar relationship exists with MAS. Additionally, our study is among the first to report on the effect of the availability of both treatment modalities and how that helps alleviate symptoms, especially in the highly symptomatic and hypertensive groups. This study demonstrates that an enhancement in the reduction in the severity of symptoms may be achieved with the availability of both

TABLE 4 Efficacy of continuous positive airway pressure (CPAP) and mandibular advancement splints (MAS) during the crossover phase as indicated by home sleep apnoea test

	Baseline	CPAP	MAS	CPAP–baseline difference (95% CI)	MAS–baseline difference (95% CI)	CPAP–MAS difference (95% CI)
Intention-to-treat analysis (n=73)						
REI, events·h ⁻¹	21.8±14.4	2.2±2.2	12.6±11.3	19.6 (16.4–22.8)*	9.2 (6.5–11.9)*	10.4 (7.8–13.0)*
ODI 3%, events·h ⁻¹	20.9±13.6	2.2±2.2	11.9±10.9	18.8 (15.8–21.8)*	9.0 (6.5–11.5)*	9.8 (7.3–12.2)*
Per-protocol analysis (n=68)						
REI, events·h ⁻¹	22.1±14.7	2.2±2.3	12.7±11.7	19.8 (15.7–24.0)*	9.4 (5.8–12.9)*	10.5 (7.7–13.3)*
ODI 3%, events·h ⁻¹	21.3±13.9	2.2±2.3	12.1±11.2	19.1 (15.2–23.0)*	9.2 (5.9–12.5)*	9.8 (7.2–12.5)*
REI supine, events·h ⁻¹	33.1±23.1	3.3±4.7	17.1±16.3	29.6 (23.4–35.8)*	16.3 (11.1–21.4)*	13.7 (10.0–17.4)*
REI non-supine, events·h ⁻¹	14.7±17.3	2.7±5.6	10.2±13.3	12.0 (6.9–17.2)*	4.5 (0.2–8.9)*	7.5 (4.6–10.4)*

Data are presented as mean±sd, unless otherwise stated. Numbers are based on sample size during the crossover phase. REI: respiratory event index; ODI: oxygen desaturation index. Mixed model for repeated measures with visit type as a fixed effect and participant as a random effect. *: statistically significant at p<0.0001.

treatments for patients to use interchangeably. This could be due to the patients being less likely to occasionally drop treatment and less likely to experience swings in AHI between one night on treatment and one night back to baseline AHI. Hence, a combination of treatments increased adherence, resulting in improved treatment outcomes. For ESS, FOSQ-10 and CFQ, the interchangeable use of therapies (6-month observation period) resulted in a higher percentage of participants achieving normal scores and a smaller percentage with persistent symptoms and functional impairment.

Despite fatigue being one of the main symptoms associated with OSA [32], it has been poorly investigated. WALIA *et al.* [33] and KAZEMEINI *et al.* [34] have shown an improvement in fatigue with CPAP (Fatigue Severity Scale questionnaire) and MAS (Checklist Individual Strength questionnaire), respectively. We demonstrated a significant reduction in fatigue (CFQ score) at all treatment time-points of 6–7 points and a greater reduction in mean scores in participants who were highly symptomatic pre-treatment (10–13 points from baseline).

Similar to the findings of WEAVER *et al.* [35], there was no statistically significant difference in the number of hours treatment was used between those who were symptomatic and asymptomatic (for ESS and FOSQ-10) at baseline (supplementary table E1). However, our results also show that participants who were more fatigued (higher baseline CFQ score) tended to use CPAP slightly more during the 1 month on CPAP. This trial is also the first to show the correlation between treatment usage and the effect on symptoms with MAS and with the alternating therapies (6-month observation period), and suggests greater improvements in daily functioning and daytime fatigue with higher adherence to treatment (albeit a weak correlation).

Both CPAP and MAS measure adherence in different ways, as their mode of administration is different. Unlike MAS adherence measurement, CPAP adherence measures various physiological phenomena. While CPAP can have mask dislodgment or air leaks and still be on the face, MAS is highly retentive to the teeth, and MAS is either properly positioned on the teeth or is out of the mouth. Therefore, MAS adherence is accurate with measurement of temperature without the measurement of leaks or residual AHI.

TABLE 5 Intention-to-treat analysis of the efficacy of continuous positive airway pressure (CPAP) and mandibular advancement splints (MAS) during the crossover phase as indicated by home sleep apnoea test in the moderate and severe obstructive sleep apnoea (OSA) groups

	Baseline	CPAP	MAS	CPAP–baseline difference (95% CI)	MAS–baseline difference (95% CI)	CPAP–MAS difference (95% CI)
Moderate OSA (n=23)						
REI, events·h ⁻¹	22.2±4.8	3.4±2.4	14.8±10.1	18.8 (14.9–22.6)*	7.4 (3.9–10.9)*	11.4 (7.9–14.9)*
ODI 3%, events·h ⁻¹	21.1±5.5	3.3±2.4	13.9±9.9	17.8 (14.0–21.7)*	7.2 (3.8–10.6)*	10.6 (7.2–14.0)*
Severe OSA (n=20)						
REI, events·h ⁻¹	40.6±9.7	2.5±2.4	19.6±14.3	38.2 (31.7–44.6)*	21.0 (14.9–27.2)*	17.1 (11.0–23.3)*
ODI 3%, events·h ⁻¹	37.5±11.1	2.5±2.4	18.6±13.5	35.0 (28.5–41.4)*	18.9 (13.0–24.7)*	16.1 (10.3–21.9)*

Data are presented as mean±sd, unless otherwise stated. REI: respiratory event index; ODI: oxygen desaturation index. Mixed model for repeated measures with visit type as a fixed effect and participant as a random effect. *: statistically significant at p<0.0001.

TABLE 6 Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10), Chalder Fatigue Questionnaire (CFQ) and 36-item Short-Form Health Survey (SF-36) questionnaire scores for the total trial population (n=68) and for the subset of participants who were highly symptomatic at baseline

	Baseline	Crossover phase		Observational phase		Significant difference in mean scores
		1-month CPAP	1-month MAS	1-month observation	6-month observation	
ESS						
Total sample	10.5±5.7	6.6±4.4	7.1±4.6	6.5±3.8	6.4±4.3	a,b,d,e
>10 (symptomatic) (n=32 (47%))	15.4±3.6	9.1±4.5	10.0±4.4	8.2±3.8	8.3±4.3	a,b,d,e
FOSQ-10						
Total sample	15.5±2.8	17.7±2.0	17.4±2.2	17.9±1.9	18.2±2.1	a,b,d,e
<17.9 (symptomatic) (n=54 (79%))	14.6±2.4	17.4±2.0	17.1±2.2	17.7±2.0	18.0±2.3	a,b,d,e
CFQ						
Total sample	16.6±5.9	10.6±4.9	10.9±5.3	10.4±4.8	10.2±5.6	a,b,d,e
>17 (symptomatic) (n=29 (43%))	22.2±3.8	10.7±5.6	11.9±6.2	9.6±5.0	10.3±6.2	a,b,d,e
SF-36: MCS						
Total sample	45.9±10.1	50.1±8.4	49.6±9.9	50.9±7.8	51.5±8.4	a,b,d,e
<36 (symptomatic) (n=14 (21%))	30.9±3.6	40.4±8.0	44.3±6.8	45.8±8.5	46.5±11.2	a,b,d,e
SF-36: PCS						
Total sample	50.1±6.6	52.3±0.8	52.6±7.2	53.4±6.2	52.7±7.1	b,d

Data are presented as mean±SD, unless otherwise stated. CPAP: continuous positive airway pressure; MAS: mandibular advancement splints; MCS: mental component summary; PCS: physical component summary. Mixed model for repeated measures with visit type as a fixed effect and participant as a random effect. Statistically significant difference in mean scores between: ^a: baseline and CPAP; ^b: baseline and MAS; ^c: CPAP and MAS; ^d: baseline and 1-month observation; ^e: baseline and 6-month observation. All are statistically significant at p<0.0001 except MCS Total sample “a,b,d,e”, MCS symptomatic “a” and PCS Total sample “b,d”, which are statistically significant at p<0.05.

The effect of a Hawthorne bias on adherence cannot be excluded, as the participants were aware that their performance was under observation. However, although the influence of being monitored was applicable throughout the trial, it was less so at the long-term follow-up. Our findings are in agreement with others who also noted the relation between initial experience and adherence, with both CPAP and MAS [30, 36]. Our study highlights the importance of a positive treatment experience and can be translated to the clinical setting by ensuring that patients have continued support and a timely resolution of problems with their CPAP or MAS. In this study, self-reported CPAP and MAS side-effects showed a reduction in frequency and intensity with time, as previously reported in the literature [37, 38]. The alternating use of therapies possibly allowed patients to partially “recover” from side-effects. The small number of dropouts in this study can be attributed to the incentive to participants, where participants were allowed to keep both treatments at no cost once they completed the study.

While this trial had many strengths, including a robust study design, objectively measured treatment adherence throughout the study and long-term follow-up, there were several limitations. The design of our study compared the adherence of two single treatments in an RCT design to the availability of two treatments. The current study was not powered to confirm the hypothesis that the 6-month availability of two treatments shows better adherence than 6 months on monotherapy, therefore further studies with the proper design and power are required. HSATs were done to assess respiratory parameters during the study instead of in-lab polysomnography due to limited access, high cost and complexity of the trial. The main limitations of HSATs include their underestimation of OSA severity due to their inability to detect hypopnoeas associated with arousals and their utilisation of total recording time instead of total sleep time in their calculation of OSA severity [39]. To help mitigate the effects of unavailability of an accurate total sleep time, our trial participants completed a sleep diary for the nights of HSAT testing. To overcome some of the other shortcomings of HSATs, scoring of the sleep studies was done centrally for all sleep studies by one sleep technologist blinded to treatment group and trial timelines.

Second, BP measures were done in-office. Future studies should assess the effect of combination therapy on 24-h BP measurements. Adherence was generally high throughout the study; this may be due to the high level of support given to the study participants. Additionally, the increased cost of purchasing two treatments cannot be easily implemented in the general population. Another limitation of this study is its generalisability, as those who agreed to participate in this study were willing to try both treatments and may not represent all OSA patients. Also, the study population of our trial showed mild sleepiness and the findings cannot be generalised to a sleepy population.

CPAP is routinely prescribed as first-line treatment for OSA with the expectation that patients will use it for the entire duration of their sleep, nightly, for the rest of their lives. This expectation lacks practicality, as evident by 40 years of data on CPAP adherence. Therefore, there is a need to improve this suboptimal adherence which proves to be a major barrier to maximising treatment effectiveness. Our results are in agreement with the findings of ALMEIDA *et al.* [40] who showed the short-term value of having both CPAP and MAS; moreover, our findings highlight the long-term value of having both treatments, especially for patients who demonstrate suboptimal adherence to CPAP, which can be detected within the first few months of therapy initiation. Furthermore, a comprehensive approach to patient management involves not only improving AHI/REI and other indices, which is necessary although not sufficient, but also involves a management strategy that can alleviate symptoms, improve quality of life and improve long-term health outcomes, while at the same time take patient preferences, lifestyle, side-effects, treatment burden and psychosocial factors into consideration. The findings of this trial show that the interchangeable use of CPAP and MAS can address many of these issues and that the availability of treatment alternatives can contribute to successful long-term management of OSA.

Conclusions

In this trial (CHOICE), there was generally high objective adherence to treatment, with participants using MAS for a greater number of hours compared to CPAP in the crossover phase. In the observational phase, the majority of participants utilised both CPAP and MAS interchangeably.

This trial proposes a change to the traditional approach in the long-term management of OSA and provides evidence supporting the necessity for having access to both CPAP and MAS for improved long-term management. Our results show that alternating therapies appears to have an important role in disease management in partnership with the patient, and that multimodality treatment can contribute to the personalisation of medicine and its tailoring to individual patient needs. The interchangeable use of therapies led to a similar improvement and comparable clinical effectiveness on patient-centred outcomes while increasing overall adherence to treatment.

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Data availability: All data needed to evaluate the conclusions in this article are present and tabulated in the main text or the supplementary material. This article is the result of an original randomised clinical trial in participants with established mild-to-severe OSA. Anonymised data might be shared upon reasonable request, please contact the corresponding author.

This clinical trial was prospectively registered before enrolment of the first participant at ClinicalTrials.gov with identifier number NCT02242617.

Ethics statement: Ethical approval was obtained by the institutional ethics board of the three universities at which the study was conducted: University of British Columbia (H14-01215), Université de Montréal (14-125-CERES-D(2)) and Université Laval (2015-2434).

Author contributions: M.M. Hamoda: writing of the original draft, review and editing of the manuscript, literature search, study design, data collection, figures, tables, data interpretation, and data verification. N. Huynh: conceptualisation, study design, data collection, data analysis, data verification, and review and editing of the manuscript. N.T. Ayas: conceptualisation, study design, and review and editing of the manuscript. P. Rompré: data analysis, study design and figures. J-F. Masse: study design and data collection. P. Arcache: study design and data collection. N. Bansback: study design, software and data acquisition. G. Lavigne: conceptualisation, study design, and review and editing of the manuscript. F. Series and J.A. Fleetham: study design, and review and editing of the

manuscript. F.R. Almeida: conceptualisation, literature search, funding acquisition, study design, data collection, data interpretation, figures, tables, data verification, and review and editing of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. M.M. Hamoda, N. Huynh and F.R. Almeida directly accessed and verified the data reported in the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of interest: N. Huynh reports support for the present study from the Canadian Institute of Health Research (CIHR), MOP-136987, made to their institution (Université de Montréal), and membership on the Board of Directors for the American Academy of Dental Sleep Medicine. N.T. Ayas reports support for the present study from the Canadian Institute of Health Research (CIHR). J-F. Masse reports support for the present study from the Canadian Institute of Health Research (CIHR), MOP-136987, made to their institution (Université de Montréal), and a leadership role as Editor for the *Journal of Dental Sleep Medicine*, for the American Academy of Dental Sleep Medicine. G. Lavigne reports support for the present study from SomnoMed and Phillips Respironics with free access to devices, grants from the Canadian Institute of Health Research (CIHR) (Canadian Government), payment or honoraria for lectures and presentations from Straumann (sleep bruxism), and receipt of equipment from Somnodent and Panthera Dental with free access to oral devices for research; G. Lavigne also serves on the Canadian Pain Task Force on Chronic Pain (Canadian Government, non-paid). F.R. Almeida reports support for the present study from Philips Respironics, SomnoMed Inc. and Braebon, grants from the Canadian Institute for Health Research (CIHR), support for attending meetings from SomnoMed, and receipt of equipment, materials, drugs, medical writing, gifts or other services from Philips Respironics, SomnoMed Inc. and Braebon. The remaining authors have no potential conflicts of interest to disclose.

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