Unterausschuss Methodenbewertung (UA MB)
Antrag der Patientenvertretung nach § 140f SGB V auf Überprüfung der Methode Unterkieferprotrusionsschiene bei leichter bis mittelgradiger obstruktiver Schlafapnoe bei Erwachsenen nach § 135 Absatz 1 SGB V

Inhalt

1. Medizinische Relevanz der obstruktiven Schlafapnoe

Das obstruktive Schlafapnoe-Syndrom (OSA) stellt eine schlafbezogene Atmungsstörung dar, die lebensbedrohliche Folgeerkrankungen nach sich ziehen kann.

Eine Schlafapnoe entsteht, wenn die Muskulatur in den oberen Atemwegen erschlafft. Dadurch verengt sich der Atemweg im Rachenbereich oder blockiert sogar ganz, wodurch beim Ein- und Ausatmen laute Schnarchgeräusche entstehen. Durch diese

Atmungsstörung wird der Körper nicht ausreichend mit Sauerstoff versorgt. Zusätzlich sinken der Puls und der Blutdruck. Das Atemzentrum im Gehirn schlägt Alarm und löst einen Weckreiz aus: Betroffene wachen kurz auf, meist ohne es zu merken. Dadurch wird der Schlafrhythmus unterbrochen, der Herzschlag erhöht sich und der Blutdruck steigt. Wiederholtes Auftreten in einer Nacht kann verhindern, in den Tiefschlaf zu fallen.

Das führende klinische Symptom der OSA ist die Tagesschläfrigkeit bis hin zum unfreiwilligen Einschlafen, wenngleich es Betroffene gibt, die keine Schläfrigkeit aufweisen oder diese als Krankheitssymptom negieren bzw. nicht explizit wahrnehmen. Tagesschläfrigkeit verursacht Leistungsdefizite und beeinträchtigt im Laufe der Erkrankung u. a. die kognitive Leistungsfähigkeit, die soziale Kompatibilität und die Lebensqualität. Fremdanamnestisch werden Atemstillstände berichtet. Der diagnostische Hauptbefund ist der Apnoe-Hypopnoe-Index (AHI), der die Anzahl der Apnoen und Hypopnoen pro Stunde Schlafzeit angibt. Er objektiviert die Diagnose und bestimmt in der Zusammenschau mit der klinischen Symptomatik und den komorbiden Erkrankungen den Schweregrad der OSA.

Faktoren, die das Auftreten von obstruktiver Schlafapnoe bestimmen, sind in erster Linie der BMI, das Alter, Geschlecht und kraniofaziale Besonderheiten. Weitere Faktoren sind Rauchen, Alkohol, Schwangerschaft, die Chemorezeptorsensitivitat im Bereich der Atmungsregulation und vorbestehende Erkrankungen wie Rheuma, Akromegalie, Hypothyreose oder das polyzystische Ovarialsyndrom (2.)

2. Diagnose

Eine OSA wird dann diagnostiziert, wenn die Atmungsstörung durch keine andere Schlafstörung oder medizinische Erkrankung oder durch Medikamente oder andere Substanzen erklärbar ist und entweder ein AHI > 15/h (Ereignis jeweils ≥ 10 s) Schlafzeit oder ein AHI ≥ 5/h Schlafzeit in Kombination mit einer typischen klinischen Symptomatik oder relevanten Komorbidität vorliegt. Ab einem AHI > 15/h und ≤ 30/h wird die Schlafapnoe als mittelgradig, ab einem AHI > 30/h als schwer eingestuft.

3. Therapieoptionen

Die **CPAP-Therapie** (continuous positive airway pressure) über Nasenmaske ist die Standardtherapie bei **mittelgradiger oder schwerer** Schlafapnoe, um die Anzahl an

Atemstillstände zu minimieren. Bei dieser Art der Therapie ist das Tragen einer Atemmaske erforderlich. Sie wird in der Regel über Mund und Nase angelegt. Bei einigen Varianten besteht auch die Möglichkeit, die Maske nur über die Nase zu ziehen. Ziel der Atemmaske ist die Verhinderung der Verengung der Atemwege. Die Atemmaske wirkt dabei so, dass während des gesamten Schlafs ein kontinuierlicher Überdruck erzeugt. Der Überdruck bewirkt, dass sich die Rachenwände und schlaffen Muskeln im Hals- und Rachenbereich nicht verengen können. Durch dieses Prinzip werden Apnoen verhindert.

Eine der größten Einschränkungen bzw. Belastungen für Patientinnen und Patienten stellt das Tragen der Atemmaske selbst dar. Neben dem ungewohnten Gefühl, beim Schlafen eine Maske zu tragen, kommen weitere Faktoren hinzu, die die Betroffenen, zumindest in der ersten Zeit, beeinträchtigen können. Das Atemgerät erzeugt einen ständigen Überdruck, gegen welchen angeatmet werden muss. Ein Schlafen in völliger Stille ist nicht mehr möglich, da das Atemgerät permanent Geräusche erzeugt.

Bei der **leichten bis mittleren** Form der Schlafapnoe steht als alleinige nicht invasive Möglichkeit die **Unterkieferprotrusionsschiene (UPS)** zur Verfügung. Alternativ wird sie auch bei Patientinnen und Patienten, die mit einer Schlafmaske (CPAP-Gerät) nicht zurechtkommen, eingesetzt. Die Betroffenen tragen nachts eine Kunststoffschiene im Mund, die den Unterkiefer und die Zunge weiter vorne hält. Hierdurch wird die Einengung des Rachenraums verringert, die Atemwege werden im Schlaf mechanisch offengehalten und der Atemwegswiderstand nimmt ab. Positive Prädiktoren für einen Behandlungserfolg sind eine Rückenlage-betonte OSA, ein guter Unterkiefervorschub und eine Obstruktion auf Zungengrundniveau (1.). Unterkieferschienen werden von Zahnärztinnen oder -ärzten und Kieferorthopädinnen und Kieferorthopäden, die Erfahrung in der Schlafmedizin haben, angepasst. Vorteile der UPS sind ein geräuschloser Einsatz und leichter Transport. Zudem wird die UPS von Patientinnen und Patienten gut toleriert (2.). (Anmerkung der Antragssteller: Die Patientenvertretung hat Zweifel, ob es sich bei der UPS um eine Methode und nicht um ein Hilfsmittel handelt. Vor dem Hintergrund der Rechtsprechung des Bundessozialgerichts (vgl. Urteil vom 8.7.2015, B 3 KR 6/14 R) erfolgt dennoch die Antragsstellung nach § 135 Abs. 1 SGB V, um die Versorgung sich zu stellen.

Eine weitere therapeutische Option stellen verschiedene **Operationen** dar, um die Atmung bei einer Schlafapnoe dauerhaft zu erleichtern. Bei den meisten Eingriffen wird

Gewebe gestrafft oder entfernt, um die Atemwege freier zu machen. Eine Operation hilft nur in einzelnen Fällen bei obstruktivem Schlafapnoe-Syndrom. Die Indikation muss präzise gestellt werden (3.).

Begleitende Maßnahmen können u.a. eine Gewichtsreduktion, die Verhinderung der Rückenlage (Lagetherapie) sowie Sport und Bewegung sein.

4. Prävalenz der Erkrankungen

Die Prävalenz einer obstruktiven Schlafapnoe in der Bevölkerung liegt bei 3–7 % der Männer und 2–5 % der Frauen[1]. Die Angaben beruhen auf internationalen Studien. Deutsche Daten liegen bislang nicht vor. Unabhängig vom Geschlecht ist bei Patientinnen und Patienten mit Erkrankungen des Herzkreislaufsystems die Prävalenz 2- bis 3-fach höher als in der Normalbevölkerung (3.).

5. Studien zur Unterkieferprotrusionsschiene

Phillips et al. (4.) untersuchten in einer randomisierten Crossover-Studie die Auswirkungen nach einmonatiger Therapie mit CPAP versus UPS. Die Studienpopulation bildeten 126 Patienten mit neu diagnostizierter OSA mit einem AHI > 10. 108 Patienten durchliefen die Studienteilnahme mit beiden Geräten, darunter 18% mit milder OSA, 50% mit moderater OSA und 32% mit schwerer OSA. Die Studie wurde als Nichtunterlegenheitsstudie durchgeführt. Primärer Endpunkt war der 24-Stunden-arteriellen Mitteldruck. Sekundäre Endpunkte waren Arterienverhärtung, subjektive Schläfrigkeit, gesundheitsbezogene Lebensqualität sowie die Fahrtüchtigkeit. Bezüglich des primären Endpunkts zeigte sich, dass die Behandlung mit UPS im Vergleich zur CPAP-Therapie nicht unterlegen ist. Keine Unterschiede zeigten sich hinsichtlich des Blutdrucks, der subjektiven Schläfrigkeit und Fahrtüchtigkeit. Dagegen verbesserte sich die gesundheitsbezogene Lebensqualität infolge der UPS-Therapie. Ein signifikanter Unterschied zeigte sich zugunsten der CPAP-Therapie gegenüber UPS hinsichtlich der Reduzierung des AHI. Die Autoren schlussfolgern auf Grundlage ihrer Ergebnisse, dass beide Therapieformen vergleichbare Ergebnisse liefern und die Behandlung mittels UPS bei milden bis moderaten OSA-Schweregeraden empfohlen werden kann.

[1] Punjabi NM. The Epidemiology of Adult Obstructive Sleep Apnea. Proceedings of the American Thoracic Society. 2008;5(2):136-143. doi:10.1513/pats.200709-155MG.

Eine Meta-Analyse von Li et al. (5.) aus dem Jahr 2013 schloss 14 Studien ein. Die Analyse zeigt, dass die Therapie mittels CPAP im Vergleich zu oraler Therapie mittels UPS zu besseren Ergebnisse hinsichtlich der Reduktion des AHI und weiteren polysomnographischen Parametern führt. Keine Unterschiede dagegen konnten hinsichtlich des Blutdrucks, der subjektiven Schläfrigkeit gemessen mittels Epworth Schläfrigkeitsskala (ESS), der gesundheitsbezogenen Lebensqualität und kognitiven Leistungsfähigkeit gezeigt werden. Darüber hinaus ergaben sich ähnliche Ergebnisse in Bezug auf die Anwendungsdauer, Behandlungspräferenz, Nebenwirkungen und Therapieabbrüchen. In Abwägung der vorliegenden Ergebnisse schlussfolgern die Autoren, dass trotz der Überlegenheit der CPAP-Therapie im Hinblick auf klinische Outcomes die Anwendung der oralen Therapie mittels UPS eine Therapiealternative ist, wenn Patientinnen und Patienten das CPAP-Gerät nicht anwenden können oder tolerieren.

Zu einer ähnlichen Schlussfolgerung gelangen auch Bratton et al. (6. und 7.), die in zwei Meta-Analysen den Vergleich zwischen CPAP und UPS, einmal im Hinblick auf den Endpunkt Blutdruck und zum anderen im Hinblick auf den Endpunkt Tagesschläfrigkeit, untersuchten. Im Ergebnis zeigt sich kein Unterschied zwischen der CPAP-Anwendung versus der UPS-Therapie bezüglich der Senkung des Blutdrucks (systolisch: -0.5mmHg, 95%-KI -2.0 – 1.0mmHg, p=0.55; diastolisch: -0.2mmHg, 95%-KI -1.6 – 1.3mmHg, p=0.82). Hinsichtlich der Tagesschläfrigkeit gemessen mittels ESS zeigt sich ein besserer Outcome durch die Anwendung des CPAP (0.8, 95% KI 0.1-1.4, p=0.015). Allerdings schlussfolgern hier die Autoren mit Verweis auf frühere Meta-Analysen, dass die Therapie mittels UPS eine geeignete Therapie für Patientinnen und Patienten darstellt, wenn die CPAP-Anwendung nicht toleriert wird.

In der aktuellen S3-Leitlinie (3.) der Deutschen Gesellschaft für Schlafforschung und Schlafmedizin (DGSM 2017) wird auf Grundlage der aktuellen Studienlage der Einsatz der Unterkieferprotrusionsschiene (UPS) als CPAP-Alternative bei Patientinnen und Patienten mit leichter bis mittelgradiger OSA empfohlen (Empfehlungsgrad A). Weiter kann der Einsatz einer UPS bei Patientinnen und Patienten mit schwergradiger Schlafapnoe, die CPAP nicht tolerieren oder ablehnen bzw. bei denen die CPAP-Therapie trotz Ausschöpfung aller unterstützenden Maßnahmen nicht eingesetzt werden kann, erwogen werden (Empfehlungsgrad C).

6. Schaden-Nutzen Abwägung

Die Studien zeigen eine vergleichbare Effektivität (CPAP versus UPS) in Bezug auf Tagesschläfrigkeit, Bluthochdruck und Lebensqualität. UPS ist somit eine Alternative bei leichter und mittelschwerer OSA. Selbst bei schwergradiger OSA bietet sie eine Alternative für Patientinnen und Patienten die CPAP nicht tolerieren.

Die Anpassung der Unterkieferprotrusionsschiene soll individuell mit zahnmedizinischer und schlafmedizinischer Expertise erfolgen. Nebenwirkungen der Schiene können Missempfindungen der Zähne und der Muskulatur sowie ein verstärkter Speichelfluss sein. Mögliche Veränderungen der Bisslage und der Zahnstellung sind regelmäßig zu überprüfen.

7. Kosten-Nutzen Bewertung

Bei der Literaturrecherche wurden keine Angaben zur Kosteneinschätzung der Methoden bzw. Studien zur Kosten-Nutzen-Bewertung gefunden, daher sind dazu keine validen Aussagen möglich.

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Health Outcomes of Continuous Positive Airway Pressure versus Oral Appliance Treatment for Obstructive Sleep Apnea

A Randomized Controlled Trial

Craig L. Phillips[1,2], Ronald R. Grunstein[2,3], M. Ali Darendeliler[4], Anastasia S. Mihailidou[5,6], Vasantha K. Srinivasan[4], Brendon J. Yee[2,3], Guy B. Marks[2,7], and Peter A. Cistulli[1,2]

[1]Department of Respiratory and Sleep Medicine and [5]Department of Cardiology, Royal North Shore Hospital, St. Leonards, Australia; [2]NHMRC Centre for Integrated Research and Understanding of Sleep, Woolcock Institute of Medical Research, Sydney Medical School, and [4]Department of Orthodontics, Sydney Dental Hospital and Faculty of Dentistry, University of Sydney, Sydney, Australia; [3]Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Sydney, Australia; [6]Kolling Medical Research Institute, Royal North Shore Hospital and University of Sydney, Sydney, Australia; and [7]Department of Respiratory Medicine, Liverpool Hospital, Sydney, Australia

***Rationale*: Continuous positive airway pressure (CPAP) and mandibular advancement device (MAD) therapy are commonly used to treat obstructive sleep apnea (OSA). Differences in efficacy and compliance of these treatments are likely to influence improvements in health outcomes.**

***Objectives*: To compare health effects after 1 month of optimal CPAP and MAD therapy in OSA.**

***Methods*: In this randomized crossover trial, we compared the effects of 1 month each of CPAP and MAD treatment on cardiovascular and neurobehavioral outcomes.**

***Measurements and Main Results*: Cardiovascular (24-h blood pressure, arterial stiffness), neurobehavioral (subjective sleepiness, driving simulator performance), and quality of life (Functional Outcomes of Sleep Questionnaire, Short Form-36) were compared between treatments. Our primary outcome was 24-hour mean arterial pressure. A total of 126 patients with moderate-severe OSA (apnea hypopnea index [AHI], 25.6 [SD 12.3]) were randomly assigned to a treatment order and 108 completed the trial with both devices. CPAP was more efficacious than MAD in reducing AHI (CPAP AHI, 4.5 ± 6.6/h; MAD AHI, 11.1 ± 12.1/h; $P < 0.01$) but reported compliance was higher on MAD (MAD, 6.50 ± 1.3 h per night vs. CPAP, 5.20 ± 2 h per night; $P < 0.00001$). The 24-hour mean arterial pressure was not inferior on treatment with MAD compared with CPAP (CPAP-MAD difference, 0.2 mm Hg [95% confidence interval, −0.7 to 1.1]); however, overall, neither treatment improved blood pressure. In contrast, sleepiness, driving simulator performance, and disease-specific quality of life improved on both treatments by similar amounts, although MAD was superior to CPAP for improving four general quality-of-life domains.**

***Conclusions*: Important health outcomes were similar after 1 month of optimal MAD and CPAP treatment in patients with moderate-severe OSA. The results may be explained by greater efficacy of CPAP being offset by inferior compliance relative to MAD, resulting in similar effectiveness.**

Clinical trial registered with https://www.anzctr.org.au (ACTRN 12607000289415).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Continuous positive airway pressure (CPAP) is considered to be the treatment of choice for obstructive sleep apnea (OSA). Oral appliance (OA) therapy, such as the mandibular advancement device (MAD), is a viable alternative with growing use, particularly in patients with milder OSA. Comparative effectiveness studies that examine multiple important health outcomes with these treatment modalities in patients with the full spectrum of OSA severity are lacking.

What This Study Adds to the Field

In the short term, health outcomes in patients with moderate to severe OSA were similar after treatment with CPAP and MAD. This was likely explained by the greater efficacy of CPAP being offset by inferior compliance relative to MAD. These findings strongly challenge current practice parameters recommending MAD treatment be considered only in patients with mild to moderate OSA. Long-term comparative effectiveness studies between CPAP and MAD that include objectively measured treatment compliance are needed to better define treatment strategies for patients with OSA.

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Author Contributions: P.A.C., R.R.G., M.A.D., G.B.M., and C.L.P. were responsible for the concept and design of the study. A.S.M., V.K.S., M.A.D., and C.L.P. were responsible for data acquisition. C.L.P., P.A.C., G.B.M., R.R.G., and A.S.M. performed the analysis and interpretation of data. C.L.P., P.A.C., and G.B.M. drafted the manuscript. All authors were responsible for revising of the manuscript for important intellectual content. C.L.P. and G.B.M. performed all statistical analyses. P.A.C., R.R.G., and M.A.D. obtained funding for the study. P.A.C., C.L.P., B.J.Y., and A.S.M. provided administrative, technical, and material support for the study. C.L.P. and P.A.C. supervised the study. C.L.P. is the guarantor.

Correspondence and requests for reprints should be addressed to Craig L. Phillips, Ph.D., Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, St Leonards, NSW 2065 Australia. E-mail: craig.phillips@sydney.edu.au

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Obstructive sleep apnea (OSA) affects up to 17% of adults in the United States. The prevalence is similar in other western and eastern populations (1). OSA is characterized by disordered breathing during sleep, resulting in sleep fragmentation and intermittent hypoxemia. Patients often suffer excessive daytime

sleepiness and many are at increased risk for motor vehicle crashes (2). Neurocognitive decline (3) and a lower self-reported quality of life (QOL) are also common. In addition, hypertension is highly prevalent and there is an increased incidence of cardiovascular mortality, stroke, and heart attack (4–6). Hence, OSA is a major public health problem, imposing a financial burden on health systems (7, 8).

The usual treatment of choice for OSA is nasal continuous positive airway pressure (CPAP) (9). Randomized controlled trials have demonstrated improvements in many health outcomes including subjective sleepiness (10), QOL (11), and blood pressure (BP) (12). Evidence also suggests that this treatment may reduce motor vehicle and driving simulator crashes (13). Long-term treatment may also reduce the incidence of cardiovascular events, at least in patients with severe OSA (14). However, despite these health-related improvements, many patients either reject treatment outright or only partially tolerate it, resulting in significant residual OSA (15). This limits the clinical effectiveness of this treatment modality.

More recently, oral appliances have proved to be an effective treatment for OSA, particularly the mandibular advancement device (MAD), which reposition the tongue and/or lower jaw to increase the dimensions of the airway lumen. Although the overall effect of these devices on sleep-disordered breathing is inferior to CPAP, their uptake and acceptance as an alternative therapy is generally higher (11). Similar to CPAP, several randomized controlled trials have reported improvements in BP (16, 17), sleepiness (18), and QOL (16).

Although several randomized trials have also directly compared CPAP with MAD (16, 19–26), outcomes are often limited to OSA alleviation and this has often been without gold standard polysomnography (20, 21). Few studies have assessed more clinically relevant health outcomes and used polysomnography to also assess treatment efficacy. Furthermore, many studies are small (19–23) or exclude patients with severe OSA (16, 20, 22), limiting the generalizability of the findings. Many studies have also not considered variation in treatment acclimatization and optimization periods (16, 19, 21, 22). Finally, because of the rapid changes in device development there are no studies that have used state-of-the-art MAD devices that are optimally titrated and applicable to current clinical practice.

In the present study, we aimed to compare the effect of CPAP and MAD treatments on health outcomes across multiple clinically relevant domains including cardiovascular function, sleepiness, driving simulator performance, and QOL. We hypothesized that the suboptimal efficacy with MAD would be counterbalanced by superior compliance relative to CPAP, resulting in similar overall alleviation of OSA. This would in turn result in similar effectiveness of both treatments for health outcomes related to OSA. The results from this study have previously been reported in the form of abstracts (27, 28).

METHODS

A randomized crossover open label study design was used to compare the health effects of 1 month of optimal treatment of OSA with CPAP versus MAD therapy. Optimal treatment was defined as attaining the highest compliance and best efficacy with each treatment under standard clinical practices.

Sample

The study was conducted at three sleep centers in Sydney, Australia (*see* online supplement). Eligibility criteria included patients with newly diagnosed OSA (apnea hypopnea index [AHI] >10 events per h); aged 20 years or older; greater than or equal to two symptoms of OSA (snoring, fragmented sleep, witnessed apneas, or daytime sleepiness); and a willingness to use both treatments. Recruitment was enriched for moderate-severe OSA. Patients were excluded for any of the following reasons: previous OSA treatment or a need for immediate treatment based on clinical judgment; central sleep apnea; a coexisting sleep disorder; regular use of sedatives or narcotics; preexisting lung or psychiatric disease; and any contraindication for oral appliance therapy (e.g., periodontal disease or insufficient dentition). Dental eligibility was assessed by an orthodontist at the Sydney Dental Hospital. All study procedures were approved by the site-specific Institutional Human Research Ethics Committees. Before consenting, patients were told they would be compensated for participating in the study by receiving the treatment device recommended by their sleep physician at no cost.

Procedures

All sleep studies were performed using full polysomnography according to standard procedures (*see* online supplement) (29). Treatment efficacy was established by polysomnography at the end of each treatment period under intention-to-treat conditions, with device use during the night being under patient control. Patients who met all eligibility criteria were randomized to both the treatment acclimatization and treatment arm orders. This was to minimize any bias related to treatment preference based on the order of treatment exposure and resulted in four randomized sequences (Figure 1).

The CPAP device used in the trial was the ResMed Autoset S8 (ResMed, Bella Vista, Australia). The MAD was the Somnodent (SomnoMed Ltd., Sydney, Australia), a custom fitted and titratable two-piece device with proved clinical effectiveness in treating OSA (17, 30, 31). The procedures for fitting, titration, and acclimatization to each device are described in detail in the online supplement. Briefly, a fixed CPAP pressure was determined using a previously validated autotitrating method based on the 95th percentile pressure that controlled most of the OSA events (32). In contrast, MAD was self-titrated by gradually advancing the device until the maximum comfortable limit of mandibular advancement was achieved. During each of the 4–6 weeks of acclimatization with each device, all patients were asked to use their device for as long as they could tolerate it on a nightly basis. After usage patterns had stabilized, treatment was considered to be optimized.

All outcomes were assessed on three occasions, at baseline before treatment acclimatization and then at the end of each of the 1-month treatment arms. The primary outcome was the difference in 24-hour mean arterial pressure (24MAP) between CPAP and MAD determined from 24-hour ambulatory BP monitoring. Secondary cardiovascular outcomes included other 24-hour ambulatory BP and central BP and arterial stiffness (SphymoCor, AtCor Medical, Ryde, Australia) (33). We also assessed neurobehavioral function and QOL using the Functional Outcomes of Sleep Questionnaire (FOSQ) (34), the Short Form-36 (SF-36) (35), the Epworth Sleepiness Score (ESS) (36), and the AusEd driving simulator (Australasian Sleep Trials Network, Australia) (37). Daily diaries were also used to monitor treatment side effects and compile subjective compliance data. After completing the trial but before knowledge of their results, patients reported their treatment preference (CPAP, MAD, either, or neither). Details of all outcome assessments are available in the online supplement.

Statistical Analysis

To ensure an adequate sample size to assess multiple unrelated outcomes, we powered the study on a BP outcome. The analysis was designed to establish noninferiority of MAD compared with CPAP for the primary outcome (24MAP). A previous study that also did not select patients on the basis of their hypertensive status showed that OSA treatment with therapeutic CPAP lowered 24MAP by 3.3 mm Hg relative to sham CPAP (38). Therefore, we assumed that we could establish noninferiority of MAD to CPAP for control of 24MAP with a noninferiority margin of 1.6 mm Hg. Based on our own data (17) we estimated a within-subject mean square error of 3.9 for 24MAP. Hence, to detect noninferiority of this outcome with 90% power, using a noninferiority margin of 1.6 mm Hg, a sample size of 108 completers was deemed to be required.

We limited our analyses to the 108 subjects who completed the trial, regardless of compliance with their assigned treatment. In an initial analysis, no acclimatization or treatment arm order effects were found (*see* online supplement). The primary hypothesis was tested by comparing the upper limit of the 95% confidence interval for the MAD-CPAP difference in 24MAP with the *a priori* noninferiority margin using the paired *t* test. All other outcomes were compared using repeated measures analysis of variance (*see* online supplement).

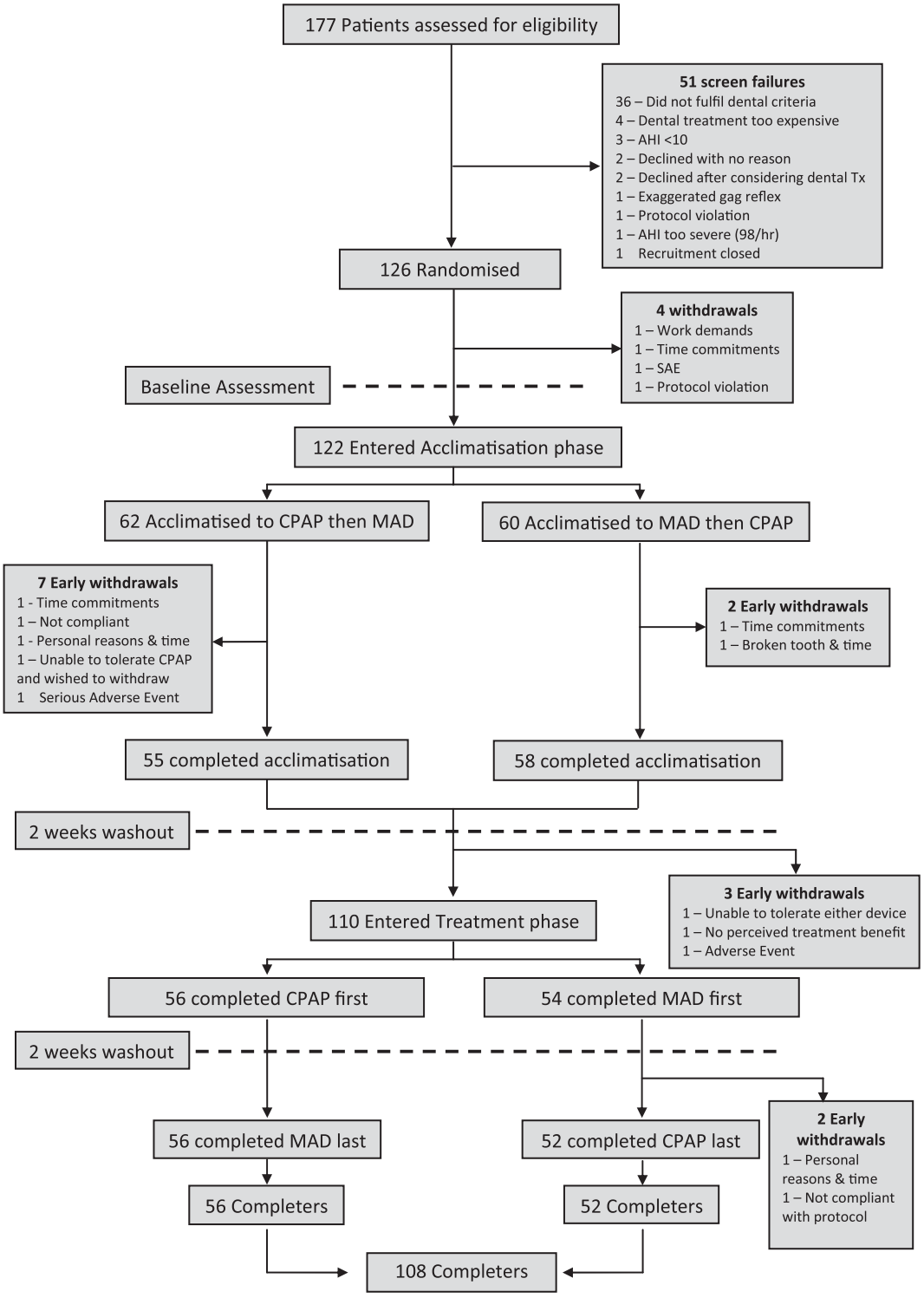

Figure 1. Study flowchart. A total of 108 patients completed the trial. Based on the separate randomization to the acclimatization phase and to the treatment phase for each of mandibular advancement device (MAD, M) and continuous positive airway pressure (CPAP, C), there were four randomization sequences with patient numbers as follows: M/C/M/C = 26; M/C/C/M = 29; C/M/C/M = 27; and C/M/M/C = 26. AHI = apnea hypopnea index; SAE = serious adverse event.

Power analysis was performed using PASS software version 11 (NCSS Inc., Kaysville, UT). All other analyses were made using the PASW statistical software version 17 (SPSS Inc., Chicago, IL).

RESULTS

Patient Flow

The patient flow through the study is detailed in Figure 1. Among the 51 screening failures, 36 patients did not fulfill dental criteria and an additional 6 declined to have the required dental work that would make them eligible for MAD treatment. Only 18 patients (14%) withdrew after randomization leaving 108 (86%) who completed the study. However, only two patients withdrew because of treatment intolerance (one CPAP and one both CPAP and MAD). None of the investigator-initiated withdrawals that were caused by adverse or serious adverse events were trial related.

Patient Characteristics

Of the 126 randomized patients, 81% were male and a majority (82%) had moderate or severe OSA with AHI greater than or

TABLE 1. BASELINE CHARACTERISTICS OF ALL RANDOMIZED PATIENTS

Variable	Mean (SD)	Range
Number randomized	126	—
Mild/moderate/severe OSA	23/69/34	—
Demographics		
M/F	102/24	—
Age, yr	49.5 (11.2)	22–78
Anthropometry		
Body mass index, kg/m^2	29.5 (5.5)	18.7–55.5
Waist circumference, cm	101.2 (15.8)	37.5–139
Neck circumference, cm	40.5 (3.8)	32–56
Sleep apnea		
AHI, h^{-1}	25.6 (12.3)	10.2–68.8
ODI, 3%	20.8 (12.5)	1.7–67.6
Sa_{O_2} T <90%	5.4 (8.8)	0–59.5
Minimum Sp_{O_2}	82.7 (7.6)	62–93
Arousal index, h^{-1}	34.3 (15.3)	8.1–79.6
Epworth Sleepiness Score	9.1 (4.2)	1–18
Office blood pressure		
Systolic	123.7 (14.1)	98–163
Diastolic	80.6 (9.1)	67–106
Medication		
Antihypertensive	48	—
Antidiabetic	7	—
Cholesterol	24	—
Reflux	15	—
Antidepressants	16	—
Antithrombotic	11	—

Definition of abbreviations: AHI = apnea hypopnea index; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; Sa_{O_2} T <90% = percentage of total sleep time spent with arterial oxygen saturation less than 90%.

Mild OSA: AHI between 5 and 15 events per hour.

Moderate OSA: AHI between 15 and 30 events per hour.

Severe OSA: AHI more than 30 events per hour.

equal to 15 per hour (Table 1). Among the 108 completers, 18% had mild OSA (AHI = 13); 50% had moderate OSA (AHI = 22); and 32% had severe OSA (AHI = 42). Hence, in the overall group 82% had moderate-severe OSA (AHI = 26; oxygen desaturation index = 21 per hour). At baseline, 50% of patients were sleepy based on an ESS greater than 10 and 38% of patients were on antihypertensive medication.

Treatment Efficacy and Preference

After titration and acclimatization with each device, the mean (SD) CPAP pressure was 10.5 ± 2 cm H_2O (range, 4–18 cm H_2O), whereas the mean mandibular advancement was 8.09 ± 2.6 mm (range, 1.1–15 mm). All metrics of sleep-disordered breathing on the intention-to-treat polysomnography night improved markedly with both treatments (Figure 2, *top*) although the improvement was greater with CPAP than MAD (Table 2). This was most evident in patients with severe OSA (*see* Figure E1 in online supplement). In total, nearly twice as many patients had complete resolution of their OSA with CPAP compared with MAD (Figure 2, *bottom*). In contrast, with MAD treatment patients reported longer sleep and higher compliance than with CPAP (Table 2). Higher compliance with MAD was consistently reported in mild, moderate, and severe OSA (*see* Figure E2). In patients where both objective and subjective CPAP compliance measures were available, objective compliance was slightly lower (objective, 4.68 ± 2 h per night; subjective, 5.1 ± 2 h per night; $P < 0.001$). Equivalent objective compliance data were not available for MAD treatment. Treatment preference results showed that 55 patients (51%) preferred MAD; 25 (23.1%) preferred CPAP; 23 (21.3%) preferred either; and 5 (4.6%) preferred neither.

BP Outcomes

In the entire group, 24-hour ambulatory BP profiles (*see* Figure E3) showed a clear sleep–wake pattern during each treatment with no apparent between-treatment differences resulting in MAD being noninferior to CPAP for control of 24MAP (mean CPAP-MAD difference [95% confidence interval], 0.2 [−0.7 to 1.1] mm Hg). However, ultimately neither treatment lowered any BP from baseline in the entire group. In contrast, in the subgroup of patients who were initially hypertensive, there were consistent treatment-related 24-hour BP improvements of between 2 and 4 mm Hg in all indexes with neither treatment having a superior effect (Figure 3; *see* Table E1). Central BP measured during pulse wave analysis also remained unchanged in the entire group (*see* Table E2) but there were reductions from baseline in arterial stiffness (aortic augmentation index) of between 1% and 2% with no between-treatment differences.

Neurobehavioral Outcomes

In contrast to BP, most neurobehavioral outcomes improved after both treatments (Table 3). In particular, there was no between-treatment difference in the improvement to subjective sleepiness (ESS) or in total and subscale measures of disease-specific QOL (FOSQ). However, MAD performed better than CPAP for improving four of eight SF-36 general QOL domains and the overall mental component score. Finally, speed deviation and reaction times to divided attention tasks during driving simulation improved to the same extent with both treatments. Figure 4 shows the ESS scores measured after acclimatization and treatment washout and after treatment (MAD or CPAP). Washout values were similar to baseline indicating a return to pretreatment sleepiness levels.

DISCUSSION

This is the largest randomized trial comparing the two leading forms of treatment for OSA on a range of unrelated health outcomes. The study has addressed many deficits from previous trials that have examined these treatments in head-to-head comparisons. Although CPAP demonstrated superior efficacy in terms of AHI reduction, self-reported compliance with MAD treatment was higher. The resulting effects on clinically important OSA-related health outcomes were either equivalent between treatments or better with MAD. Notably, these outcomes were achieved in the context of moderate to severe OSA. Overall, the comparable impact of both treatments on health outcomes has potential implications for clinical practice and future research.

Efficacy and Compliance

In all previous randomized trials that have directly compared CPAP with MAD, both treatments are shown to alleviate OSA but CPAP is consistently superior to MAD, particularly in patients with severe OSA (16, 19–26). In contrast, no studies have yet shown that nightly usage of CPAP is superior to MAD. In fact, results either favor MAD (16, 22) or do not favor either treatment (20, 21, 26). On this basis, we hypothesized that comparable outcomes between treatments would be achieved because the well-known superior efficacy of CPAP in alleviating OSA would be offset by inferior compliance relative to MAD. Indeed, our efficacy and compliance data and the resultant outcomes support this hypothesis. Finally, we have also confirmed the finding from most studies showing a clear patient preference for MAD therapy (20, 21, 23, 24, 27). These results are likely to have an important bearing on treatment effectiveness.

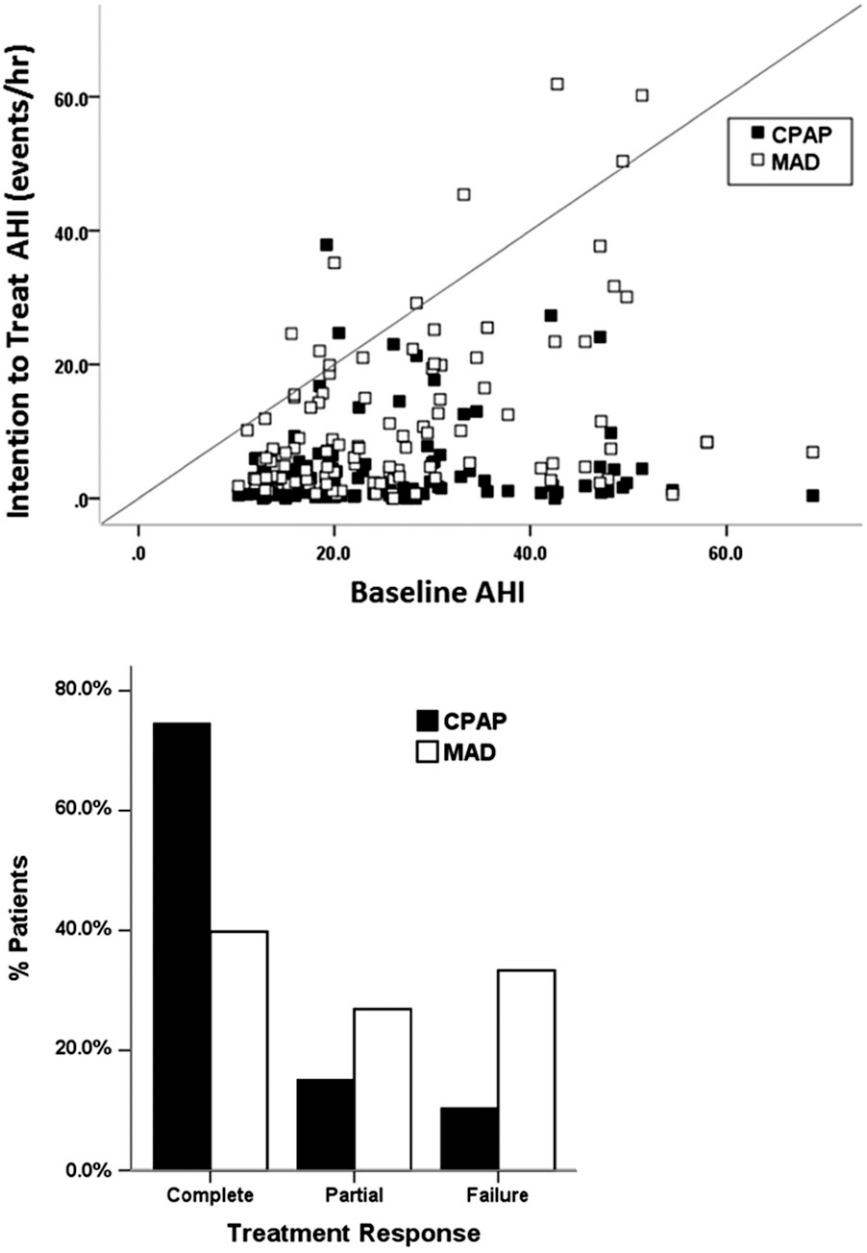

Figure 2. Overall treatment response. (*Top*) Baseline versus intention-to-treat apnea hypopnea index (AHI) for continuous positive airway pressure (CPAP) and mandibular advancement device (MAD). (*Bottom*) Treatment response based on intention-to-treat AHI for CPAP and MAD where complete response equals AHI reduced to less than five per hour, partial response equals AHI reduced by more than 50% but still more than five per hour, and failure equals AHI reduced by less than 50%. Intention-to-treat AHI data include all assessed patients regardless of treatment use on the night.

BP and Arterial Stiffness

In this trial we could only demonstrate clear improvements in BP in patients who were hypertensive at baseline. However, no improvements were evident with either treatment in the whole group. In this context, hypertensive status together with sleepiness, OSA severity, and treatment compliance have all been proposed to influence BP responses to treatment (39). Apart from hypertension, however, we do not believe that any of these other factors explain the lack of change in BP after treatment because we could not find any correlation between changes in any BP outcome with any of these factors (data not shown). The literature indicates that treatment-related improvements in BP are at best relatively small (2–3 mm Hg), even in patients with hypertension (32). It follows that demonstrating any BP improvement is difficult, particularly if the prevalence of untreated hypertension turns out to be lower than expected, as occurred in our study. However, we have demonstrated that both treatments were associated with small reductions in arterial stiffness and neither treatment proved superior. Arterial stiffness has increasingly been shown to improve cardiovascular risk stratification (40, 41) and both uncontrolled (33, 42) and randomized controlled studies (43, 44) have shown improvements after CPAP. Overall, our results point to the need for further comparative effectiveness studies that specifically target patients with hypertension.

Neurobehavioral Function and QOL

Overall, this study has found that improvements with MAD in sleepiness, QOL, and driving simulator performance were as good as or better than CPAP. Previous studies that have compared subjective sleepiness and QOL after treatment with oral appliance and CPAP therapies have either favored CPAP (21, 24) or have shown similar effects between treatments (16, 23, 25, 26). However, in the studies that favored CPAP, nonadjustable oral appliances were used and these may have been inferior to fully adjustable models, as used in our study. We found in the whole group that neither treatment had a superior effect in reducing subjective sleepiness determined from the ESS score. Additional analyses in patients who were sleepy (ESS $\geq$10) or who had severe OSA (AHI $>$30)

TABLE 2. INTENTION-TO-TREAT POLYSOMNOGRAPHY AND SELF-REPORTED COMPLIANCE

Variable	Mean (SD) CPAP	Mean (SD) MAD	*P* Value
Polysomnography			
AHI, h^{-1}	4.5 (6.6)	11.1 (12.1)	<0.0001
ODI 3%, h^{-1}	6.0 (9.7)	9.0 (11.6)	0.0001
Min Sp_{O_2}, %	90.6 (5.0)	87.2 (5.9)	<0.0001
Sp_{O_2} T90, % total sleep time	5.8 (16.9)	6.6 (15.7)	0.04
Arousal index, h^{-1}	16.6 (10.6)	19.2 (11.6)	0.02
Sleep latency, min	11.5 (15.7)	15.3 (21.3)	0.002
Sleep efficiency, %	82 (12)	82 (12)	0.9
Diary data			
Subj compliance, h/night	5.2 (2.0)	6.5 (1.3)	<0.0001
Subj sleep, h/night	6.9 (0.9)	7.1 (0.7)	0.005

Definition of abbreviations: AHI = apnea hypopnea index; compliance (h/night) = total hours of use divided by the number of nights with access to treatment; CPAP = continuous positive airway pressure; Min Sp_{O_2} = minimum arterial oxygen saturation; ODI = oxygen desaturation index; Sp_{O_2} T90 = % total sleep time below 90% arterial oxygen saturation; Subj = subjective (self-reported).

Polysomnography data include all assessed patients regardless of treatment use on the night.

also indicated a comparable improvement between treatments (data not shown). Furthermore, neither treatment was superior for improving disease-specific QOL determined from the overall and subscale scores in the FOSQ. This is consistent with two other studies (16, 25). In contrast, our study is the first to show that MAD treatment was superior to CPAP for improving four of eight SF-36 domains. Finally, we have shown in over 100 patients that driving simulator performance improves equally between oral appliance and CPAP therapies. One small study examined driving simulator performance between 9 patients treated with oral appliances and 10 patients treated with CPAP and found a similar result (45). Hence, the data that suggest that CPAP treatment reduces the risk of motor vehicle crashes may also apply for MAD treatment (46). Overall, our data support more widespread use of MAD treatment for OSA.

Study Strengths

The variations in health outcomes found in previous trials comparing CPAP with MAD are likely caused by multiple factors. These include the exclusion in some studies of patients with severe OSA (16, 20, 22); small sample sizes (<50 patients) (19–23); high dropout rates (>20%) (16, 20); nonadjustable oral appliances (21); and suboptimal compliance with CPAP therapy (<4 h) (16). In addition, the acclimatization and optimization periods with each device may have varied from one patient to another but were often included as part of the treatment period (16, 19, 21, 22). Our trial was designed to address many of these deficiencies. In addition, we believe that our choice to power the study using a noninferiority design with mean BP as the outcome has given us some degree of confidence that we would have the statistical power to examine multiple clinically important health outcomes. We also deliberately enriched our study population with patients with moderate to severe OSA including those with associated comorbid hypertension and sleepiness. Our findings in this context suggest that the clinical role of MAD treatment should be extended beyond the currently accepted mild to moderate OSA range (American Academy of Sleep Medicine practice parameters [47]). Importantly, our protocol design ensured that all patients were fully acclimatized and optimally titrated with both devices over the same timeframe before commencing the interventions. Hence, every patient had equal opportunity for exposure to both treatments. Furthermore, we randomized the order of acclimatization and intervention to reduce the risk of compliance being altered by treatment order exposure. In the end we achieved an objective CPAP compliance (4.6 h) that was comparable or better than previous trials and despite the demanding protocol, our dropout rate was only 15%.

Study Limitations

There are several limitations that should be considered in relation to our study. First, we acknowledge that the interpretation of our results is limited to patients that are eligible and willing to trial both treatments. In this context we found that 20% of

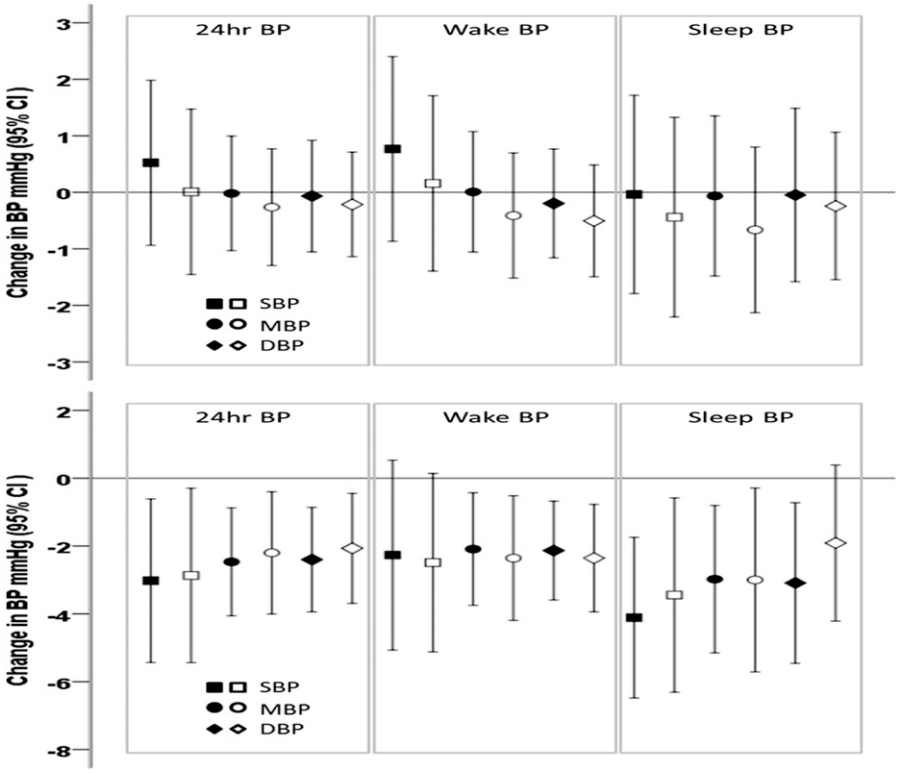

Figure 3. Change from baseline in 24-hour blood pressure (BP) variables. Data represent mean differences from baseline (95% confidence interval [CI]) on continuous positive airway pressure (CPAP) (*closed symbols*) and mandibular advancement device (MAD) (*open symbols*) for the 24-hour wake and sleep periods. (*Top*) All completers (n = 108). (*Bottom*) Hypertensive completers (n = 45) where baseline hypertension was defined as 24-hour systolic blood pressure (SBP) greater than 130 and/or 24-hour diastolic blood pressure (DBP) greater than 80 mm Hg (54). MBP = mean blood pressure.

TABLE 3. SLEEPINESS, QUALITY OF LIFE, AND DRIVING SIMULATOR PERFORMANCE (N = 108)

Variable	Baseline Mean (SE)	CPAP Mean (SE)	MAD Mean (SE)	Mean Baseline − CPAP Difference (95% CI)	Mean Baseline − MAD Difference (95% CI)	Mean CPAP − MAD Difference (95% CI)
Sleepiness and quality of life						
ESS	9.1 (0.4)	7.5 (0.4)	7.2 (0.4)	1.6 (1.0 to 2.2)*	1.9 (1.4 to 2.5)*	0.31 (−0.2 to 0.9)
FOSQ	16.3 (0.2)	17.3 (0.2)	17.3 (0.2)	−1.0 (−1.4 to −0.6)*	−1.0 (−1.4 to −0.6)*	−0.03 (−0.4 to 0.3)
Activity	3.08 (0.06)	3.3 (0.05)	3.3 (0.05)	−0.21 (−0.31 to −0.12)*	−0.24 (−0.34 to −0.15)*	−0.03 (−0.4 to 0.3)
Vigilance	3.10 (0.06)	3.32 (0.05)	3.33 (0.06)	−0.21 (−0.30 to −0.13)*	−0.23 (−0.33 to −0.13)*	−0.02 (−0.1 to 0.06)
Intimacy	3.15 (0.08)	3.35 (0.08)	3.34 (0.08)	−0.20 (−0.35 to −0.05)†	−0.19 (−0.35 to −0.03)†	0 (−0.1 to 0.2)
Productivity	3.43 (0.04)	3.6 (0.04)	3.6 (0.04)	−0.17 (−0.26 to −0.09)*	−0.19 (−0.27 to −0.11)*	−0.02 (−0.09 to 0.06)
Social	3.57 (0.05)	3.76 (0.05)	3.73 (0.05)	−0.18 (−0.28 to −0.08)*	−0.15 (−0.26 to −0.05)*	0.03 (−0.07 to 0.13)
SF-36						
Physical function	82.3 (1.8)	83.7 (1.9)	84.7 (1.9)	−1.4 (−4.5 to 1.7)	−2.4 (−5.7 to 0.9)	−1.3 (−3.7 to 1.0)
Role physical	70.4 (3.4)	81.7 (3.2)	79.9 (2.9)	−11.3 (−17.6 to −5.1)*	−9.5 (−15.2 to −3.7)*	1.9 (−4.6 to 8.3)
Bodily pain	76.5 (2.2)	76.2 (2.1)	81 (1.9)	0.3 (−4.2 to 4.8)	−4.5 (−8.4 to −0.5)†	−4.8 (−8.7 to −0.9)†
General health	63.1 (2.0)	65.7 (1.9)	67.4 (2.0)	−2.6 (−5.5 to 0.3)	−4.3 (−7.0 to −1.6)*	−1.7 (−4.1 to 0.7)
Vitality	48.9 (2.1)	56.3 (2.2)	60.1 (2.0)	−7.4 (−10.8 to −3.9)*	−11.2 (−14.8 to −7.6)*	−3.8 (−7.7 to −0.02)†
Social function	77.6 (2.3)	79.7 (2.2)	84.8 (1.8)	−2.1 (−6.1 to 1.9)	−7.2 (−10.9 to −3.5)*	−5.1 (−8.9 to −1.3)*
Role emotional	65.1 (4)	78.8 (3.3)	81.6 (2.9)	−13.7 (−21.7 to −5.7)*	−16.5 (−23.5 to −9.5)*	−2.8 (−8.4 to 2.8)
Mental health	71.7 (1.5)	72.6 (1.6)	75.3 (1.5)	−1.0 (−3.5 to 1.6)	−3.6 (−5.9 to −1.3)*	−2.6 (−5.1 to −0.2)†
Physical component	68.1 (1.8)	72.6 (1.7)	74.4 (1.6)	−4.4 (−7.0 to −1.9)*	−6.3 (−8.9 to −3.7)*	−2.0 (−4.5 to 0.6)
Mental component	71.5 (2.2)	77.1 (2)	80.6 (1.8)	−5.6 (−9.4 to −1.7)*	−9.1 (−12.4 to −5.7)*	−3.5 (−6.7 to −0.3)†
AusEd driving						
Mean RT to DAT, s	1.05 (0.03)	0.98 (0.03)	0.97 (0.03)	0.07 (0.007 to 0.13)†	0.07 (0.02 to 0.13)†	0.004 (−0.05 to 0.06)
Lapses	0.16 (0.06)	0.32 (0.15)	0.26 (0.12)	−0.16 (−0.47 to 0.15)	−0.11 (−0.34 to 0.13)	0.06 (−0.06 to 1.8)
Crashes	0.25 (0.09)	0.22 (0.06)	0.14 (0.04)	0.03 (−0.13 to 0.19)	0.12 (−0.04 to 0.27)	0.1 (−0.04 to 0.24)
Mean lane deviation, cm	59.1 (2.3)	59.6 (2.3)	58.7 (2.4)	−0.51 (−4.1 to 3.0)	0.4 (−2.9 to 3.7)	1.01 (−1.7 to 3.7)
Mean speed deviation	3.0 (0.26)	2.39 (0.18)	2.45 (0.20)	0.62 (0.31 to 0.93)*	0.56 (0.15 to 0.96)*	−0.04 (−0.31 to 0.22)

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Score; FOSQ = Functional Outcomes of Sleep Questionnaire; MAD = mandibular advancement device; RT to DAT = reaction time to divided attention task; SF-36 = Short Form-36.

* $P < 0.01$.

† $P < 0.05$.

assessed patients were not eligible for trialing MAD, whereas all patients were able to trial CPAP. We also recognize that we had no objective measure of MAD compliance, because this was not available at the time the study was conducted. We have therefore assumed that the small discrepancy between objective and subjective CPAP compliance would be similar with MAD, making a between-treatment comparison of self-reported compliance valid. In fact, new research using a novel technology for measuring long-term objective MAD compliance (48) has found no difference between objective and subjective compliance. This may indicate that our MAD-CPAP compliance difference was underestimated making the true night-night residual AHI more equal between treatments. Furthermore, we acknowledge that our measure of treatment efficacy (on-treatment AHI) may be slightly underestimated during polysomnography because there were a small number of patients whose AHI was largely determined without CPAP or MAD treatment. This was despite all patients being strongly encouraged to use treatment on the night of polysomnography. It is also possible that the use of auto CPAP titration followed by fixed pressure treatment may have resulted in suboptimal efficacy (AHI reduction) and/or compliance. However, comparable improvements in OSA have previously been shown when comparing auto with manual titration (49) and compliance with auto versus fixed CPAP has been shown to be similar (50). In our study, the AHI on CPAP during the end of treatment polysomnography was 4.5 events per hour and overall objective compliance was 4.7 hours. Hence, we do not believe that efficacy or compliance was compromised by our approach to CPAP titration or the use of a fixed pressure. In fact, we chose to use a fixed pressure because it may be more effective in lowering BP (51).

In this study we found that overall neither treatment seemed to improve BP from baseline, which likely relates to the normotensive status of most participants. This then limits the ability to claim true noninferiority for BP control. Regardless, we believe our decision to pursue a noninferiority analysis for BP was well founded. Noninferiority designs rely on the premise that the active control (in this case CPAP) has superior efficacy to placebo as established in previous trials (52). Based on meta-analyses of randomized trials (12, 53), we believed this has been adequately demonstrated, even in trials in which elevated BP was not a specific inclusion criterion (17, 38), which was the case in this study. It could also be argued that our treatment periods were relatively short, limiting the impact on BP. However, studies using similar treatment periods have reported significant treatment effects. Ultimately our crossover design made the study challenging and time

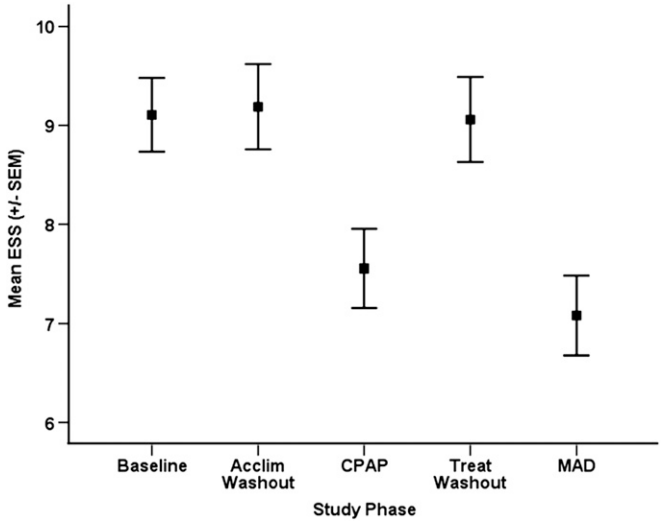

Figure 4. Epworth Sleepiness Score (ESS) at baseline, after continuous positive airway pressure (CPAP) or mandibular advancement device (MAD) treatment, and after acclimatization and treatment washout periods.

consuming for our patients and extending the treatment periods would have negatively impacted the feasibility of completing such a large study. The finding of a significant treatment effect among patients who were hypertensive at baseline is an indication that the treatment period was of sufficient duration. Furthermore, we observed very clear therapeutic effects from each treatment for important neurobehavioral and QOL outcomes that were either comparable or favored MAD. Sleepiness, which is arguably the main factor motivating patients to seek OSA treatment, showed clear clinical improvement and deterioration after initiation and withdrawal of either treatment. Finally, we cannot claim that the improvements in health outcomes would be sustained in the long term, or indeed whether BP may deteriorate because of partially effective treatment. Further long-term studies with objective assessment of compliance with both devices will clarify how true night-to-night residual OSA impacts on health outcomes.

Conclusions

This short-term study has demonstrated that the health outcomes in patients with moderate to severe OSA were similar after treatment with CPAP and MAD. The results are likely explained by the greater efficacy of CPAP being offset by inferior compliance relative to MAD resulting in a similar "treatment" AHI with each device. These findings strongly challenge current practice parameters that recommend that MAD treatment should only be considered in patients with mild to moderate OSA or in those who have failed or refuse CPAP treatment. Our findings provide a strong rationale for a long-term comparative effectiveness study of these two treatment modalities. It is hoped that such studies will allow a rigorous evidence-based approach to changing current treatment recommendations.

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Comparison of CPAP and Oral Appliances in Treatment of Patients With OSA: A Systematic Review and Meta-analysis

Wenyang Li MD, Lin Xiao PhD, and Jing Hu PhD

BACKGROUND: A systematic review and meta-analysis was performed to compare the outcomes of oral appliances (OAs) with those of CPAP in treatment of patients with obstructive sleep apnea (OSA). METHODS: Relevant studies were retrieved from the following electronic databases, up to and including September 2012: MEDLINE, PubMed, EMBASE, and Central Register of Controlled Trials. The main outcomes were Epworth Sleepiness Scale score, health-related quality of life, cognitive performance, blood pressure, apnea-hypopnea index (AHI), arousal index, minimum S_{pO_2}, percent rapid eye movement sleep, treatment usage, side effects, treatment preference, and withdrawals. RESULTS: Fourteen trials were finally included in this review. Our results demonstrated that the effects on Epworth Sleepiness Scale score ($P = .31$ and .09 in crossover and parallel-group trials), health-related quality of life, cognitive performance, and blood pressure of OAs and CPAP were similar. Besides, pooled estimates of crossover trials suggested a significant difference in favor of CPAP regarding AHI ($P < .001$), arousal index ($P = .001$), and minimum S_{pO_2} ($P < .001$), while pooled estimates of parallel-group trials showed a significant difference in favor of CPAP regarding AHI ($P < .001$) and percent rapid eye movement sleep ($P = .02$). Moreover, OAs and CPAP yielded fairly similar results in terms of treatment usage ($P = .26$ for hours/night in crossover trials, and $P = .14$ for hours/night and $P = .19$ for nights/week in parallel-group trials), treatment preference, side effects, and withdrawals ($P = .34$ in parallel-group trials). CONCLUSIONS: CPAP yielded better polysomnography outcomes, especially in reducing AHI, than OAs, indicating that OAs were less effective than CPAP in improving sleep-disordered breathing. However, similar results from OAs and CPAP in terms of clinical and other related outcomes were found, suggesting that it would appear proper to offer OAs to patients who are unable or unwilling to persist with CPAP. *Key words: oral appliances; CPAP; obstructive sleep apnea; meta-analysis.* [Respir Care 2013;58(7):1184–1195. © 2013 Daedalus Enterprises]

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstruction of the upper airway, often resulting in oxygen desaturation and arousal from sleep.[1] Excessive daytime sleepiness, snoring, reduction in cognitive function, and the risk of developing long-term vascular consequences are among the common symptoms of this condition.[2] There is now a considerable body of literature documenting the pathophysiology and consequences of OSA; however, the morbidity, benefits of treatment, and optimal mode of management of OSA remain a clinical dilemma.

CPAP has been proposed as the most effective treatment for OSA. Applying CPAP during the night is effec-

Drs Li and Hu are affiliated with the State Key Laboratory of Oral Diseases, Department of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, China. Dr Xiao is affiliated with the Department of Oral and Maxillofacial Surgery, Central Hospital of Fuling, Fuling, Chongqing, China.

Drs Li and Xiao contributed equally to this study, and are co-first authors.
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Correspondence: Jing Hu PhD, State Key Laboratory of Oral Diseases, Department of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan 610041, China. E-mail: drhu@vip.sohu.com.

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tive in reducing symptoms of sleepiness and improving quality of life measurements in people with OSA.[3] However, CPAP is a constraining treatment with frequent local adverse effects that can constitute an obstacle to regular and prolonged use of the apparatus,[4] so individuals may abandon or adhere poorly to this therapy. Of OSA patients in whom CPAP is recommended, 5–50% reject this treatment and 12–25% of the remaining patients can be expected to discontinue CPAP,[5,6] and the milder the symptoms of OSA, the less likely are the subjects to accept CPAP. Besides, although there is no doubt that CPAP is usually very effective, increased healthcare costs with this treatment may be another important factor that affects its adherence in patients with OSA.[7]

Oral appliances (OAs) have emerged as an increasingly popular alternative for CPAP over the past decade.[8] The rationale behind the use of OAs is unclear, but is probably multifactorial, involving both a structural change with enhancement of the caliber of the airway and also triggering of stretch receptors, which activate the airway support muscles.[9] Several studies have demonstrated that OAs can effectively reduce the severity of sleep-disordered breathing and lead to symptomatic improvement, and patients seem to be more adherent to OAs than to CPAP.[10,11]

Many randomized trials have compared the outcomes of OAs versus CPAP in the treatment of patients with OSA,[10-15] most of which indicate that OAs are less effective in reducing AHI but are preferred over CPAP. However, none of these trials has been large enough to confirm the outcomes within subgroups. Therefore, a meta-analysis that allows for the pooling and quantification of results from different studies is required to overcome this limitation. The present systematic review and meta-analysis was performed to compare the outcomes of OAs with those of CPAP.

QUICK LOOK

Current knowledge

Both CPAP and oral appliances have been used for the treatment of obstructive sleep apnea. CPAP is more effective at reducing the apnea-hypopnea index, but oral appliances are better tolerated.

What this paper contributes to our knowledge

This meta-analysis of 14 comparative trials suggests that CPAP reduces apnea-hypopnea index and is more effective than oral appliances. There were no differences in treatment usage, treatment preference, side effects, or study withdrawals between CPAP and oral appliance.

Methods

Search Strategy

A computerized search of PubMed (1966 to May 2012), EMBASE (1984 to May 2012), and the Cochrane Controlled Trials Register (2nd quarter, 2012) was carried out. The search strategy consisted of a combination of key words concerning the therapies (continuous positive airway pressure, CPAP, oral appliance, OA) and the disease (obstructive sleep apnea, OSA). These key words were used as MESH headings and free text words. All searches were limited to humans, clinical trial, review and meta-analysis. In addition, manual searching of reference lists from potentially relevant papers was performed, based on the computer-assisted strategy, to identify any additional studies that might have been missed.

Selection of Studies

Using a pre-defined protocol, 2 reviewers (LW and XL) independently selected studies for evaluation. Disagreements were resolved through consensus decision. The inclusion criteria were:

- Compared the outcomes of an OA versus CPAP in the treatment of patients with OSA
- Prospective and randomized
- Published in English and full-text available
- All data were included only once (replication was not permitted). Trials with nonclinical outcomes (eg, cephalometry) were excluded.

Data Extraction

Two reviewers independently performed the data extraction. For each trial, the following items were collected: first author, year of publication, design of the study, subject demography (number, mean age, and sex ratio), details of the inclusion criteria, types of OAs, types of CPAP devices, and study duration. The relevant outcomes pooled in this analysis included Epworth Sleepiness Scale (ESS), health-related quality of life, cognitive performance, blood pressure, apnea-hypopnea index (AHI), arousal index, minimum S_{pO_2}, percent rapid eye movement sleep, treatment usage (including nights/week and hours/night), side effects, subject preference, and withdrawals.

Heterogeneity

A test for heterogeneity (Cochrane Q) was performed to identify inconsistency in the study results. However, because the test is susceptible to the number of trials included in the meta-analysis, we also calculated I^2. This statistic, which is directly calculated from the Q statistic, describes the percentage of variation across the studies that is due to heterogeneity rather than change. I^2 ranges from 0% to 100%, with 0% indicating the absence of any heterogeneity. Although absolute numbers for I^2 are not available, values $< 50\%$ are considered low heterogeneity. When I^2 is $< 50\%$, low heterogeneity is assumed, and the effect is thought to be due to change. Conversely, when I^2 exceeds 50%, then heterogeneity is thought to exist and the effect is random.

Assessment of Risk of Bias

Two independent investigators evaluated the risk of bias of the included studies according to the Collaboration's recommended tool (section 8.5 in chapter 8).[16] Briefly, the risk of bias of each study was assessed by using the following methodological components: randomization and generation of the allocation sequence; allocation concealment; subject blinding and examiner blinding; and description of the follow-up. The details of each methodological item are shown in Table 1. However, the subjects knew which treatment they received, because the appearance of the OAs were obviously different from that of the CPAP devices, and it was impossible to make these treatment devices look alike, so blinding and allocation concealment could not be easily performed, and thus the trials with an adequate method of randomization and clear description of the follow-up were considered to be of low risk of bias. Besides, a particular concern with the crossover trials is the risk of a carry-over effect, which occurs when an intervention given in the first period has an effect that carries over into the second period and may influence subjects' responses in the subsequent period. Therefore, crossover trials with a wash-out period between treatments were generally regarded as having low risk of a carry-over effect.[17]

Table 1. Methodological Variables

Randomization
Adequate: referred to a random number table; used a computer random number generator; coin toss; shuffled cards or envelopes; threw dice; drew lots; minimization.
Unclear: insufficient information about the sequence generation process to permit judgment of low risk or high risk.
Inadequate: sequence generated by odd or even date of birth; sequence generated by some rule based on date of admission; sequence generated by some rule based on hospital or clinic record number.
Allocation concealment
Adequate: central allocation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
Unclear: insufficient information to permit judgment of low risk or high risk.
Inadequate: used an open random allocation schedule; assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
Patient blinding
Adequate: no blinding or incomplete blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding; blinding of subjects and key study personnel ensured, and unlikely that the blinding could have been broken.
Unclear: insufficient information to permit judgment of low risk or high risk.
Not performed, if the trial was not double blind.
Examiner blinding
Adequate: no blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Unclear: insufficient information to permit judgment of low risk or high risk.
Not performed, if the trial was not double blind.
Withdrawals and Dropouts
Adequate: the number of and reasons for dropouts and withdrawals in all intervention groups were described, or it was specified that there were no dropouts or withdrawals.
Unclear: insufficient reporting of attrition/exclusions to permit judgment of low risk or high risk (eg, number randomized not stated, no reasons provided for missing data).
Inadequate: the number of and reasons for dropouts and withdrawals were not described.

Statistical Analysis

We conducted the meta-analysis with statistics software (Revman 5.1, Cochrane Collaboration, Oxford, United Kingdom). Results are expressed as risk ratios and/or odds ratios with 95% CIs for dichotomous outcomes, and as mean differences with 95% CIs for continuous outcomes. For crossover trials the analyses for continuous outcome variables were conducted by using the generic inverse variance statistical method, where mean differences and standard errors were entered. A correlation coefficient of 0.5 was used throughout this meta-analysis to estimate the standard errors for some crossover trials, where the appropriate standard deviation of differences was not included in study reports. Sensitivity analyses were performed to assess the impact of the assumed correlation coefficient on the outcomes of meta-analyses by repeating the analyses assuming correlation coefficients of 0.3 and 0.7, respectively. A fixed effects model was initially used; however, we planned to use a random effects model if there was evidence of significant heterogeneity across trials ($P < .10$

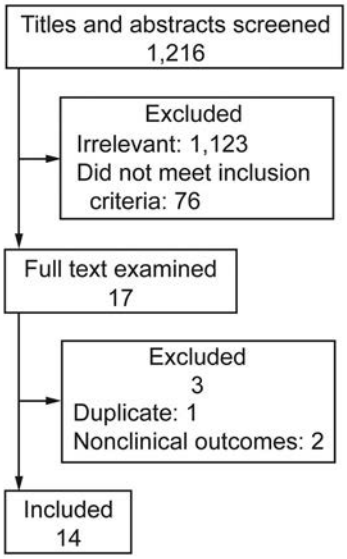

Fig. 1. Flow of study identification, exclusion, and inclusion.

and $I^2 > 50\%$). A sensitivity analysis was performed to explore the potential source of heterogeneity. We also planned to use funnel plot asymmetry to assess for publication bias.

Results

Figure 1 shows the details of study identification, inclusion, and exclusion. The literature search yielded 1,216 articles. By screening the titles and abstracts, 1,123 papers were excluded due to the irrelevance to this topic. In 93 potentially relevant references, 17 papers were taken for a comprehensive evaluation. After retrieving the full articles, one was excluded because of duplicated data[18] and 2 were excluded because of nonclinical outcomes.[19,20] Finally, 14 studies were included in this meta-analysis.[10-15,21-28] Among these studies, 8 trials had a crossover design,[10-12,15,21-23,27] and 6 had a parallel-group design.[13,14,24-26,28] The main characteristics of the included studies are shown in Table 2.

Risk of Bias in These Trials

The assessment of risk of bias in all included studies is shown in Table 3. A method of block randomization was used in 6 trials.[14,22,24-26,28] Adequate method for allocation concealment was applied in 3 trials.[14,27,28] In one trial,[28] the subjects remained blinded to the nature of therapy, and examiner blinding was performed in 3 trials.[22,27,28] The description of follow-up was considered adequate in all included trials. So over half of the included trials, with 3 or more methodological components inadequate or unclear, were regarded as having a high risk of bias. A washout period between treatments was described in 6 of the 8 crossover trials,[10,12,15,21,23,27] and those 6 were considered to have a low risk of carry-over effect.

Clinical Outcomes

Score of Epworth Sleepiness Scale. There were 5 crossover trials[12,15,21-23] and 3 parallel-group trials[13,14,24] reporting the score of ESS. The test for heterogeneity detected a significant heterogeneity across the crossover trials ($P < .001$, $I^2 = 88\%$), while there was no evidence of heterogeneity across the parallel-group trials ($P = .85$, $I^2 = 0\%$). Pooled estimates revealed that there was no significant difference between treatments, both in crossover trials (mean difference 0.74, 95% CI −0.69 to 2.17, $P = .31$) and in parallel-group trials (mean difference 1.33, 95% CI −0.19 to 2.85, $P = .09$) (Fig. 2).

Health-Related Quality of Life. Two crossover trials[12,22] reported the data on the Functional Outcomes of Sleepiness Questionnaire, and pooled estimates showed no significant difference between groups (mean difference −0.43, 95% CI −1.41 to 0.54, $P = .38$), but with a significant heterogeneity across the trials ($P = .008$, $I^2 = 86\%$) (see Fig. 2). There were 2 crossover trials[12,22] and 3 parallel-group trials[13,14,28] reporting the outcome of the 36-item Medical Outcomes Study Short Form questionnaire (SF-36). In the trial by Engleman et al,[22] CPAP-treated subjects had significantly higher SF-36 scores for the health transition and mental components ($P = .001$ and .008, respectively), while there were no significant difference in the SF-36 physical component scores between treatments. Barnes et al[12] reported that there was no significant difference regarding SF-36 mean scores between the groups. Two parallel-group trials[13,14] reported component scores from the SF-36, and pooled estimates revealed no significant difference regarding each component score between treatments. Aarab et al[28] reported that the changes in the domains of the SF-36 were not significantly different between groups. One crossover trial[22] and one parallel-group trial[14] reported the data on Hospital Anxiety and Depression Scale, both of which showed that the Hospital Anxiety and Depression Scale scores did not differ significantly between treatments.

Cognitive Performance. There were 3 crossover trials reporting the outcome of cognitive performance. In the trial by Engleman et al[22] it was shown that no significant differences in performance intelligence-quotient decrement score, Trail Making Test B, Steer Clear Performance Test, and Paced Auditory Serial Addition Test 2s correct was detected between treatments. Barnes et al[12] reported that there was no significant difference regarding the cognitive function assessed by Paced Auditory Serial Addition

Table 2. Main Characteristics of Included Studies

First Author	Year	Study Design	*n*	Age y	Male %	Inclusion Criteria AHI, events/h	Oral Appliance	CPAP Device(s)	Study Duration
Ferguson[10]	1996	Crossover	27	46.2	88.9	15–50	Anterior mandibular positioner (Snore-Guard, Hays & Meade, Albuquerque, New Mexico)	Nasal CPAP (REMstar Choice or Tranquility Plus, Respironics, Murrysville, Pennsylvania)	2 × 16 weeks Washout period 2 weeks
Ferguson[21]	1997	Crossover	24	44.0	79.2	15–50	Anterior mandibular positioner (Snore-Guard)	Nasal CPAP (REMstar Choice or Tranquility Plus)	2 × 16 weeks Washout period 2 weeks
Randerath[11]	2002	Crossover	20	56.5	80.0	5–30	ISAD (intraoral sleep apnea device) (IST, Hinz, Herne, Germany)	CPAP (Max II, MAPData, ResMed, San Diego, California) (Somnotron, Weinmann, Hamburg, Germany) (Vector, Hoffrichter, Schwerin, Germany)	2 × 6 weeks Washout period 0 weeks
Engleman[22]	2002	Crossover	48	46.0	75.0	≥ 5 ESS score ≥ 8	Mandibular repositioning splints	CPAP Device not stated	2 × 8 weeks Washout period 0 weeks
Tan[23]	2002	Crossover	24	50.9	83.3	≤ 50	Mandibular advancement splint (Erkodent, Tuttlingen, Germany)	Nasal CPAP (REMstar Choice) (Sullivan Elite, ResMed, San Diego, California)	2 × 16 weeks Washout period 2 weeks
Barnes[12]	2004	Crossover	114	47.0	80.0	5–30	Mandibular advancement splint (Medical Dental Sleep Appliance, RJ and VK Bird, Middle Park, Victoria, Australia)	Nasal CPAP (Sullivan Elite)	3 × 12 weeks Washout period 2 weeks
Hoekema[24]	2007	Parallel	10 10	47.6 49.7	77.7 90.0	> 5	Oral appliance (Thornton Adjustable Positioner type 1, Airway Management, Dallas, Texas)	CPAP (PV10, Breas, Mölnlycke, Sweden)	12 weeks
Hoekema[25]	2007	Parallel	21 27	48.0 51.0	100.0 100.0	≥ 5	Oral appliance (Thornton) Adjustable Positioner type 1	CPAP (PV10)	12 weeks
Lam[13]	2007	Parallel	34 34	45.0 45.0	76.5 79.4	5–40 ESS score > 9	Oral appliance made of dental acrylic modified from a Harvold-type functional activator	CPAP (ARIA LX, Respironics, Murrysville, Pennsylvania)	10 weeks
Hoekema[14]	2008	Parallel	51 52	48.8 49.4	84.3 94.2	≥ 5	Oral appliance (Thornton) Adjustable Positioner type 1	CPAP (PV10)	12 weeks
Hoekema[26]	2008	Parallel	15 13	89.3	49.7	> 20	Oral appliance (Thornton) Adjustable Positioner type 1	CPAP (PV10)	12 weeks
Gagnadoux[15]	2009	Crossover	59	50.3	86.8	10–60	Mandibular advancement device (AMC, Artech Medical, Pantin, France)	CPAP (Sullivan S6 Elite, ResMed, San Diego, California)	2 × 8 weeks Washout period 1 week
Trzepizur[27]	2009	Crossover	12	46.0	100.0 100.0	≥ 15	Mandibular advancement device (AMC)	CPAP (Sullivan S6 Elite)	2 × 8 weeks Washout period 1 week
Aarab[18]	2011	Parallel	21 22	50.4 54.9	81.0 68.2	5–45 ESS score ≥10	Mandibular advancement device with adjustable protrusive mandibular positioner at a constant vertical dimension	Nasal CPAP (REMstar Pro)	48 weeks

AHI = apnea and hypopnea index
ESS = Epworth Sleepiness Scale

Test 1.2 between CPAP and OA. Gagnadoux et al[15] reported that CPAP and OAs both improved the trail making test A and trail making test B, but with no significant difference between groups.

Table 3. Risk of Bias in the Included Studies

First Author	Year	Randomization	Allocation Concealment	Patient Blinding	Examiner Blinding	Follow-up
Ferguson[10]	1996	Yes/unclear	Unclear	Unclear	Unclear	Clear report
Ferguson[21]	1997	Yes/unclear	Unclear	Unclear	Unclear	Clear report
Randerath[11]	2002	Yes/unclear	Unclear	Unclear	Unclear	Clear report
Engleman[22]	2002	Yes/adequate	Unclear	Unclear	Yes/adequate	Clear report
Tan[23]	2002	Yes/unclear	Unclear	Unclear	Not performed	Clear report
Barnes[12]	2004	Yes/inadequate	Unclear	Unclear	Unclear	Clear report
Hoekema[24]	2007	Yes/adequate	Unclear	Not performed	Not performed	Clear report
Hoekema[25]	2007	Yes/adequate	Unclear	Not performed	Not performed	Clear report
Lam[13]	2007	Yes/unclear	Unclear	Unclear	Unclear	Clear report
Hoekema[14]	2008	Yes/adequate	Adequate	Not performed	Not performed	Clear report
Hoekema[26]	2008	Yes/adequate	Unclear	Not performed	Not performed	Clear report
Gagnadoux[15]	2009	Yes/unclear	Unclear	Unclear	Unclear	Clear report
Trzepizur[27]	2009	Yes/unclear	Adequate	Unclear	Yes/adequate	Clear report
Aarab[18]	2011	Yes/adequate	Adequate	Blinded to the nature of therapy	Yes/adequate	Clear report

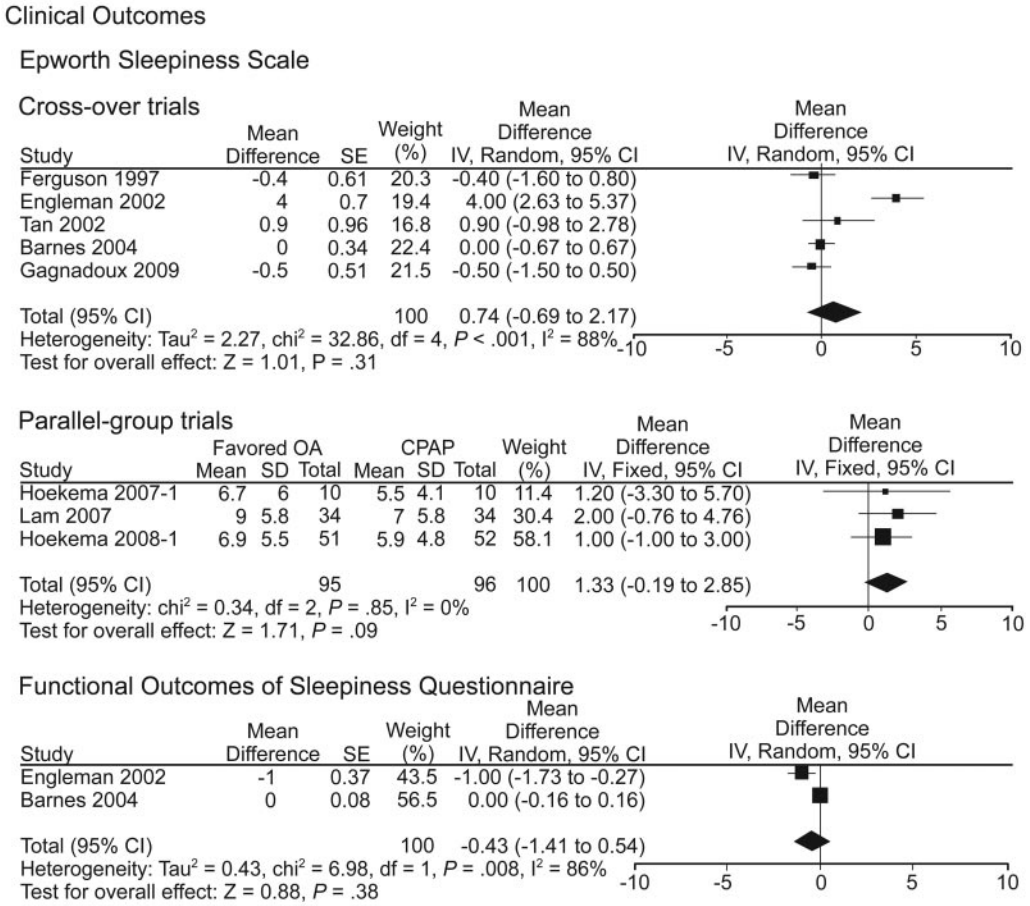

Fig. 2. Forest plot of the meta-analysis of clinical outcomes. IV = inverse variance.

Blood Pressure. Two crossover trials and one parallel-group trial reported the outcome of blood pressure. In the trial by Engleman et al[22] it was reported that, although there was no significant response in the 24-hour mean systolic or diastolic blood pressure between groups, OA-treated subjects had a significantly lower nighttime dia-

stolic blood pressure ($P < .05$). However, Trzepizur et al[27] and Lam et al[13] both reported no significant difference in blood pressure change between OA and CPAP.

Polysomnography Outcomes

Apnea Hypopnea Index. There were 6 crossover trials[10-12,21-23] and 3 parallel-group trials[13,14,28] reporting AHI. The test for heterogeneity revealed a significant heterogeneity across the crossover trials ($P = .008$, $I^2 = 68\%$), while no evidence of heterogeneity was detected across the parallel-group trials ($P = .41$, $I^2 = 0\%$). Overall, OA-treated subjects had significantly more apneas and hypopneas, both in the crossover trials (mean difference 8.25, 95% CI 5.89–10.61, $P < .001$) (Fig. 3) and the parallel-group trials (mean difference 5.96, 95% CI 3.40 to 8.51, $P < .001$) (see Fig. 3).

Arousal Index. Five crossover trials[10-12,21,23] and 2 parallel-group trials[13,28] reported arousal index. Pooled estimates of the crossover trials found a significant difference in favor of CPAP (mean difference 3.10, 95% CI 1.23–4.96, $P = .001$), but with a significant heterogeneity across the trials ($P = .06$, $I^2 = 55\%$) (see Fig. 3). While the pooled estimates of the parallel-group trials revealed no significant difference between treatments (mean difference 3.18, 95% CI –1.17 to 7.52, $P = .15$), the results were robust and there was no heterogeneity across the trials ($P = .32$, $I^2 = 0\%$) (see Fig. 3).

Minimum S_{pO_2}. There were 4 crossover trials[10-12,21] and 4 parallel-group trials[13,14,25,26] reporting minimum S_{pO_2}. Pooled estimates of crossover trials showed that OA-treated subjects had a significantly lower minimum S_{pO_2} (mean difference −5.11%, 95% CI −6.91 to –3.30, $P < .001$), but there was substantial heterogeneity across the trials ($P = .003$, $I^2 = 78\%$) (see Fig. 3). However, pooled estimates of the parallel-group trials found no significant difference between treatments (mean difference −0.94, 95% CI –2.50 to 0.62, $P = .24$), with no evidence of heterogeneity across the trials ($P = .14$, $I^2 = 45\%$) (see Fig. 3).

Rapid Eye Movement Sleep. Four crossover trials[10,11,21,23] and 2 parallel-group trials[14,28] reported the outcome of percent rapid eye movement sleep. The test for heterogeneity detected significant heterogeneity across the crossover trials ($P < .001$, $I^2 = 84\%$), and pooled estimates found no significant difference between treatments (mean difference −0.27, 95% CI –3.75 to 3.22, $P = .88$) (see Fig. 3). While the pooled estimates of the parallel-group trials showed a significant difference in favor of CPAP (mean difference 2.42, 95% CI 0.31 to 4.53, $P = .02$), there was no heterogeneity across the trials ($P = .97$, $I^2 = 0\%$) (see Fig. 3).

Other Related Outcomes

Treatment Usage. There were 2 crossover trials[12,22] reporting treatment usage of hours/night, and 4 parallel-group trials[13,14,25,26] reporting treatment usage of hours/night and nights/week. There was significant heterogeneity across the crossover trials ($P < .001$, $I^2 = 95\%$, hours/night) and across the parallel-group trials ($P < .001$ and $I^2 = 93\%$ for hours/night, and $P = .09$ and $I^2 = 54\%$ for nights/week). The pooled estimates showed no significant difference between treatments both in the crossover trials (mean difference 1.01, 95% CI −0.75 to 2.78, and $P = .26$ for hours/night) (Fig. 4) and in the parallel-group trials (mean difference 0.82, 95% CI −0.27 to 1.91, and $P = .14$ for hours/night, and mean difference 0.16, 95% CI −0.08 to 0.40, and $P = .19$ for nights/week) (see Fig. 4).

Treatment Preference. Five crossover trials reported the outcome of treatment preference. The trials by Ferguson et al[10,21] reported that most subjects who were treated successfully preferred CPAP to OAs, but OA was preferred as a long-term treatment among these subjects. Engleman et al[22] reported that a 5-variable model explained 68% of the variance in treatment preference, and eventually identified 83% and 90% of subjects, respectively, preferring OA and CPAP. Barnes et al[12] reported that the overall percentages of preferred treatment were 30% for OA and 44% for CPAP. While Gagnadoux et al[15] reported that 71.2% of subjects preferred OA, 8.5% preferred CPAP, and 8 subjects had no treatment preference.

Side Effects. There were 6 crossover trials and 2 parallel-group trials reporting side effects. Ferguson et al[10,21] found mild side effects common with OA, including sore teeth, sore jaw muscles, and excessive salivation, while CPAP-treated subjects more commonly had moderate to severe side effects, such as nasal congestion, rhinorrhea, eye irritation, and a sense of suffocation. Randerath et al[11] reported that CPAP-treated subjects often had a sense of pressure on the face, while OA-treated subjects often had early morning discomfort in the mouth. Engleman et al[22] reported that side effects were common both for OAs and CPAP; however, some side effects were treatment-specific, such as dental pain or salivation with OA, and stuffy nose or mask problems with CPAP. Gagnadoux et al[15] reported that the mean side effects scores were similar for OA and CPAP in the subjects who completed the study ($P = .80$). Lam et al[13] and Aarab et al[28] both reported that

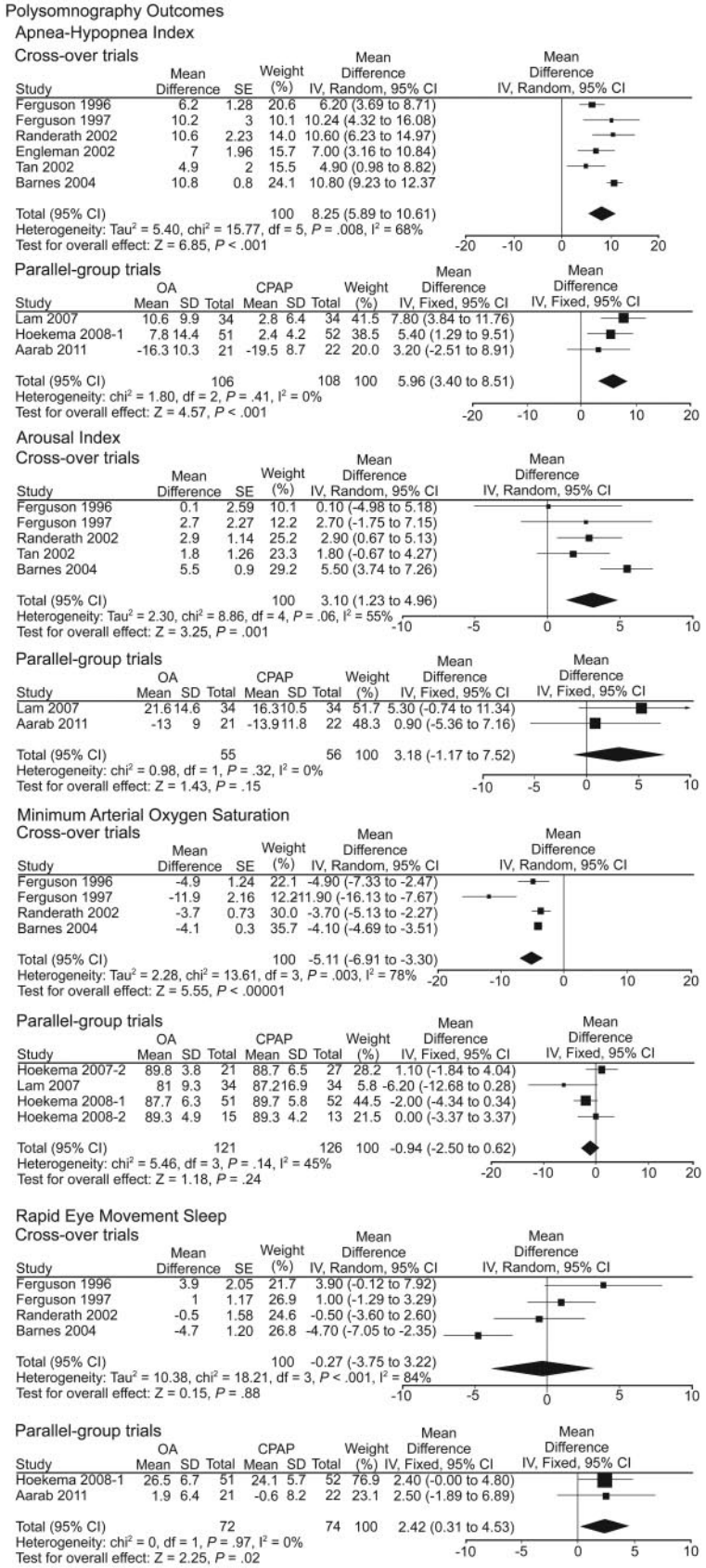

Fig. 3. Forest plot of the meta-analysis of polysomnography outcomes. IV = inverse variance.

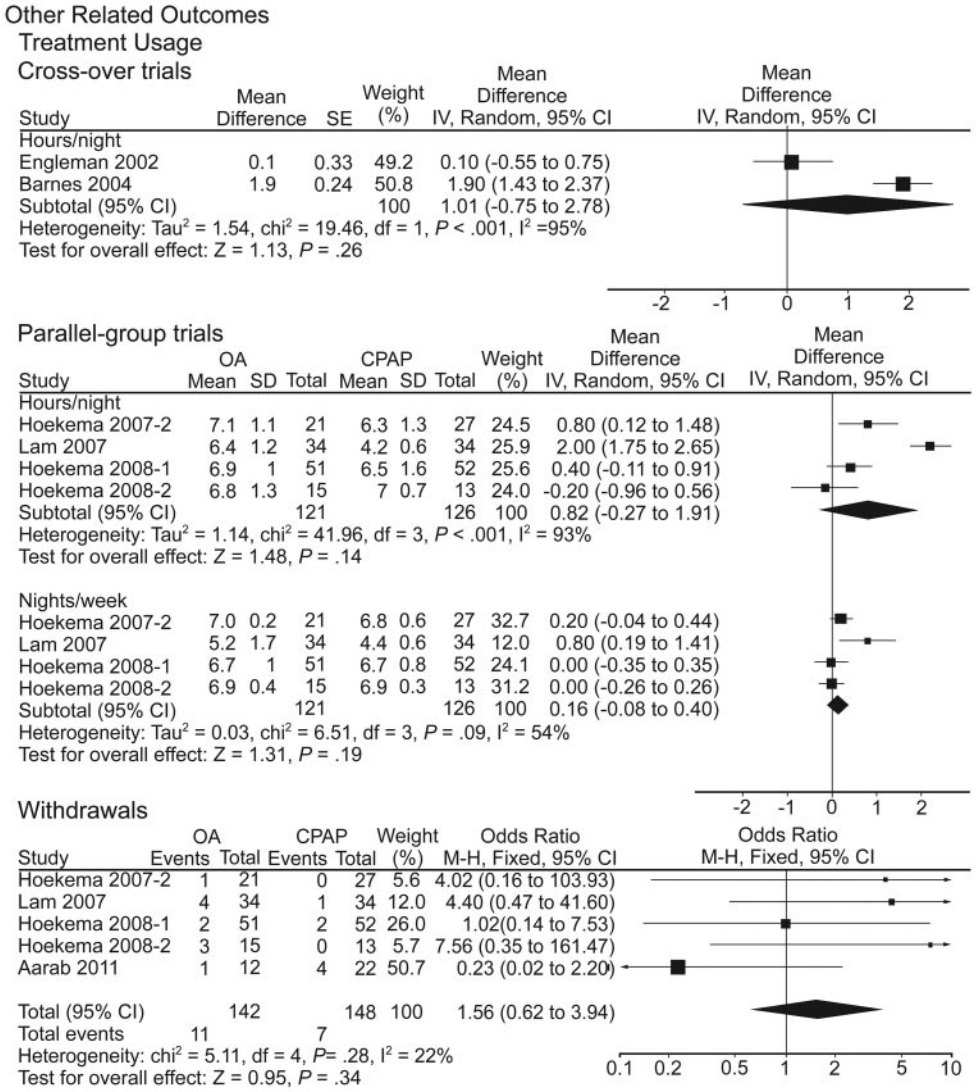

Fig. 4. Forest plot of the meta-analysis of other related outcomes. IV = inverse variance. M-H = Mantel-Haenszel.

nearly all subjects reported side effects, but that all side effects were considered mild and acceptable.

Withdrawals. Ferguson et al[10] reported that one subject dropped out during the wash-in period and one dropped out in the OA treatment period. In another trial by Ferguson et al,[21] one subject withdrew in the OA treatment period and 3 refused to cross over to the CPAP treatment arm. Tan et al[23] and Gagnadoux et al[15] both reported that 2 subjects dropped out in the CPAP treatment period and one withdrew in the OA treatment period. Trzepizur et al[27] reported one dropout from the CPAP group. Five parallel-group trials reported withdrawals,[13,14,25,26,28] and the pooled estimates showed no significant difference between treatments (odds ratio 1.56, 95% CI 0.62–3.94, $P = .34$), with no evidence of heterogeneity ($P = .28$, $I^2 = 22\%$) (see Fig. 4).

Discussion

Although many randomized trials have supported the evidence that CPAP is more effective than OAs in reducing OSA,[10-15] some studies have suggested that the efficacy of OAs in modifying the health risks associated with OSA is somewhat similar to that of CPAP.[29] A previous Cochrane review[8] showed that OAs were less effective than CPAP in reducing AHI and improving minimum S_{pO_2} during sleep; however, subjects seemed to be more adherent to OAs than CPAP in a small part of the included trials. So the prior Cochrane review led to the conclusion that CPAP seemed to be more effective than OAs in improving sleep-disordered breathing, but the difference in symptoms between these 2 treatments was not significant.

However, the results of the prior Cochrane review were not completely convincing. The main reason was that nearly

Table 4. Sensitivity Analysis for the Heterogeneity of Crossover Trials

	Study That Was the Major Contributor to the Heterogeneity	Heterogeneity After Excluding the Study			Pooled Estimates of the Remaining Studies		
		Chi-square	*P*	I^2 %	Mean Difference (95% CI)	Z	*P*
Epworth Sleepiness Scale	Engleman[22]	2.02	.57	0	–0.12 (–0.61 to 0.36)	0.50	.62
Apnea-hypopnea index	Barnes[12]	5.23	.26	24	7.05 (5.41–8.68)	8.43	< .001
Arousal index	Barnes[12]	1.18	.76	0	2.24 (0.76–3.73)	2.96	.003
Minimum S_{pO_2}	Ferguson[21]	0.71	.70	0	–4.08 (–4.61 to –3.55)	15.08	< .001
Percent rapid eye movement sleep	Tan[23]	2.90	.23	31	1.07 (–0.61 to 2.74)	1.25	.21

all the included crossover trials in the prior Cochrane review did not report any paired results, though they did provide means and SDs for the outcomes of each treatment. In this case, paired analyses from these crossover trials could only be approximated by assuming a certain degree of correlation between the 2 treatment outcomes. The reviewers used a correlation coefficient of zero, which was equivalent to a parallel group analysis of the results. The limitation by doing this involved the fact that the particular strength of crossover design was ignored, where treatments were evaluated on the same subjects, allowing comparison at the individual rather than the group level.[30] Therefore, the validity of the pooled estimates of the crossover trials in the prior Cochrane review needed further confirmation.

In the present systematic review and meta-analysis, a correlation coefficient of 0.5 was used to estimate the standard errors for some included crossover trials, where the appropriate standard deviations of the differences were not included in the study reports. Our results demonstrated that OA-treated subjects had similar ESS scores, when compared to CPAP-treated subjects, both in crossover ($P = .31$) and parallel-group ($P = .09$) trials. In addition, the effects of OAs and CPAP on health-related quality of life, cognitive performance, and blood pressure were also similar, but CPAP may produce a better outcome than OA. From the above results, it can be concluded that OAs and CPAP yield fairly similar results in terms of these clinical outcomes.

As for the polysomnography (PSG) outcomes, the pooled estimates of the crossover trials suggested a significant difference in favor of CPAP with regard to AHI ($P < .001$), arousal index ($P = .001$), and minimum S_{pO_2} ($P < .001$). The pooled estimates of parallel-group trials showed that, compared with CPAP-treated subjects, OA-treated subjects had significantly more apneas and hypopneas ($P < .001$). Moreover, a significant difference in favor of CPAP was detected regarding percent rapid eye movement sleep ($P = .02$). The above results may lead to a conclusion that CPAP yielded better PSG outcomes than OAs, especially in reducing AHI. Treatment success with OA, defined as an AHI of < 5 events/hour, was found in 19–75% of the subjects. An AHI of < 10 events/hour was reported in 30–94% of the subjects. However, CPAP reduced AHI more efficiently and gave a higher success rate in all these studies.[10-15,21-23] Overall, these PSG outcomes (especially hypoxia) are of crucial importance with regard to survival and morbidity in subjects with OSA, which emphasizes the relevance of optimal suppression of respiratory disturbances and argues against OA's treatment effect on OSA in terms of these respiratory parameters,[31,32] indicating that OAs can be given only for those who refuse CPAP.

As far as other related outcomes were concerned, the pooled estimates revealed no significant difference between OA and CPAP with regard to treatment usage ($P = .26$ for hours/night in the crossover trials, and $P = .14$ for hours/night and $P = .19$ for nights/week in the parallel-group trials) and withdrawals ($P = .34$ in the parallel-group trials).

Side effects were common with both OAs and CPAP, with a similar severity across treatments. Moreover, although the subjects generally preferred OA to CPAP, similar preferences for OA and CPAP were reported. The above results lead us to draw the conclusion that OA-treated subjects have similar results regarding all these related outcomes, when compared with CPAP-treated subjects.

Although a substantial heterogeneity was detected in all pooled estimates of crossover trials, it could be eliminated by the sensitivity analysis. After excluding the major contributors to the heterogeneity, the pooled estimates still got the same results regarding all these outcomes (Table 4), indicating that the heterogeneity did not have a significant effect on the pooled estimates of the crossover trials. In addition, a sensitivity analysis performed by repeating the analyses assuming correlations of 0.3 and 0.7 revealed that the assumed correlation of 0.5 did not affect the pooled estimates of the crossover trials with regard to all these outcomes (Table 5). While the heterogeneity across the

Table 5. Sensitivity Analysis for Crossover Trials, With 2 Assumed Correlation Coefficients

	Number of Trials	Number of Subjects	Pooled Estimates			Heterogeneity		
			Mean Difference (95% CI)	Z	*P*	Chi-square	*P*	I^2 %
Assuming a Correlation Coefficient of 0.3								
Epworth Sleepiness Scale	5	272	0.77 (–0.67 to 2.20)	1.05	.30	54.99	< .001	93
Functional Outcomes of Sleepiness Questionnaire	2	165	–0.41 (–1.38 to 0.55)	0.84	.40	5.13	.02	81
Apnea-hypopnea index	6	260	8.23 (5.85–10.62)	6.76	< .001	18.93	.002	74
Arousal index	5	209	3.59 (2.25–4.93)	5.26	< .001	6.40	.17	38
Minimum S_{pO_2}	4	185	–5.01 (–6.60 to –3.42)	6.17	< .001	15.41	.002	81
Percent rapid eye movement sleep	4	95	–0.24 (–3.69 to 3.21)	0.13	.89	28.57	< .001	90
Treatment usage, h/night	2	165	1.01 (–0.76 to 2.77)	1.12	.26	31.24	< .001	97
Assuming a Correlation Coefficient of 0.7								
Epworth Sleepiness Scale	5	272	0.72 (–0.72 to 2.15)	0.98	.33	23.37	< .001	83
Functional Outcomes of Sleepiness Questionnaire	2	165	–0.46 (–1.43 to 0.52)	0.92	.36	10.54	.001	91
Apnea-hypopnea index	6	260	8.27 (5.93 to 10.62)	6.91	< .001	13.67	.02	63
Arousal index	5	209	2.94 (1.08 to 4.80)	3.10	.002	14.12	.007	72
Minimum S_{pO_2}	4	185	–5.14 (–7.08 to –3.21)	5.20	< .001	12.17	.007	75
Percent rapid eye movement sleep	4	95	–0.30 (–3.80 to 3.21)	0.17	.87	13.41	.004	78
Treatment usage, h/night	2	165	1.02 (–0.74 to 2.78)	1.13	.26	14.06	< .001	93

parallel-group trials was slight, most of the evidence from the analyses should be considered robust. But there was substantial heterogeneity in the analysis of treatment usage, the major contributor to heterogeneity was the study by Lam et al.[13] By removing this study the heterogeneity was eliminated ($P = .16$ and $I^2 = 46\%$ for hours/night, and $P = .47$ and $I^2 = 0\%$ for nights/week), and the pooled estimates indicated a significant difference in favor of OA in treatment usage of hours/night ($P = .04$), but there was still no significant difference in treatment usage of nights/week between treatments ($P = .29$).

Nevertheless, the present systematic review and meta-analysis still had several potential limitations. One potential limitation was that the degree of mandibular advancement by the OAs and the OA designs were variable among the included trials, which caused uncertainty regarding comparisons between these studies. A second potential limitation involved the fact that most of the included trials had high risk of bias, due to 3 or more unclear or inadequate methodological components. Moreover, a few of the included crossover trials[11,22] had a high risk of a carry-over effect, due to the absence of a wash-out period between treatments.

A third limitation was the small sample sizes of all the included trials and the small number of studies. A funnel plot for pooled estimates to assess the potential publication bias was not performed, and unpublished studies with negative results could not be identified, so there might be publication bias as well, which could result in overestimation of the effectiveness of the interventions.

Conclusions

CPAP has yielded better PSG outcomes than OA, especially lower AHI, indicating that OAs are less effective than CPAP in improving sleep-disordered breathing. If sleep-disordered breathing is left inadequately controlled, the long-term risk of systemic morbidity associated with OSA may be substantial, which may also suggest that CPAP is more reliable than OA in treatment of OSA. However, similar results from OA and CPAP in terms of clinical and other related outcomes were found, including ESS score, health-related quality of life, and treatment usage. Based on this evidence it would appear proper to offer OA to patients who are unable or unwilling to persist with CPAP.

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Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis

Daniel J Bratton, Thomas Gaisl, Christian Schlatzer, Malcolm Kohler

Summary

Background Excessive daytime sleepiness is the most important symptom of obstructive sleep apnoea and can affect work productivity, quality of life, and the risk of road traffic accidents. We aimed to quantify the effects of the two main treatments for obstructive sleep apnoea (continuous positive airway pressure and mandibular advancement devices) on daytime sleepiness and to establish predictors of response to continuous positive airway pressure.

Methods We searched MEDLINE and the Cochrane Library from inception to May 31, 2015, to identify randomised controlled trials comparing the effects of continuous positive airway pressure, mandibular advancement devices or an inactive control (eg, placebo or no treatment) on the Epworth Sleepiness Scale (ESS, range 0–24 points) in patients with obstructive sleep apnoea. We did a network meta-analysis using multivariate random-effects meta-regression to assess the effect of each treatment on ESS. We used meta-regression to assess the association of the reported effects of continuous positive airway pressure versus inactive controls with the characteristics of trials and their risk of bias.

Findings We included 67 studies comprising 6873 patients in the meta-analysis. Compared with an inactive control, continuous positive airway pressure was associated with a reduction in ESS score of 2·5 points (95% CI 2·0–2·9) and mandibular advancement devices of 1·7 points (1·1–2·3). We estimated that, on average, continuous positive airway pressure reduced the ESS score by a further 0·8 points compared with mandibular advancement devices (95% CI 0·1–1·4; p=0·015). However, there was a possibility of publication bias in favour of continuous positive airway pressure that might have resulted in this difference. We noted no evidence that studies reporting higher continuous positive airway pressure adherence also reported larger treatment effects (p=0·70).

Interpretation Continuous positive airway pressure and mandibular advancement devices are effective treatments for reducing daytime sleepiness in patients with obstructive sleep apnoea. Continuous positive airway pressure seemed to be a more effective treatment than mandibular advancement devices, and had an increasingly larger effect in more severe or sleepier obstructive sleep apnoea patients when compared with inactive controls. However, mandibular advancement devices are an effective alternative treatment should continuous positive airway pressure not be tolerated.

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Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland (D J Bratton PhD, T Gaisl MD, C Schlatzer MD, M Kohler MD); **and Zurich Centre for Integrative Human Physiology** (M Kohler), **Centre for Interdisciplinary Sleep Research** (M Kohler), **University of Zurich, Zurich, Switzerland**

Correspondence to: Prof Malcolm Kohler, Department of Pulmonology, University Hospital Zürich, 8091 Zürich, Switzerland **malcolm.kohler@usz.ch**

Introduction

Obstructive sleep apnoea is a common disorder characterised by repetitive arousals from sleep due to upper airway obstruction that often leads to increased daytime sleepiness. Investigators have estimated that the prevalence of symptomatic obstructive sleep apnoea can range from between 3% to more than 30% in the adult population with the disease being more common in men than in women.[1,2] One of the most frequent symptoms of obstructive sleep apnoea is increased daytime sleepiness, which can lead to reduced work productivity and quality of life and increased risk of road traffic accidents.[3,4] Daytime sleep propensity in obstructive sleep apnoea is most commonly measured using the Epworth Sleepiness Scale[5] (ESS), which is a self-administered questionnaire assessing a person's level of daytime sleepiness and average sleep propensity in eight typical daytime scenarios. Each scenario is scored either 0 (would never doze), 1 (slight chance of dozing), 2 (moderate chance of dozing), or 3 (high chance of dozing). The scores are then totalled to give an overall score between 0 and 24 with ESS scores ≤10 being regarded as normal.[6,7] Despite its subjective nature, the ESS is a widely accepted and commonly used instrument in clinical studies and daily clinical practice because it is simple to complete, easy to apply and score, and possesses high reproducibility and internal consistency.[6,8]

Continuous positive airway pressure is regarded as the gold-standard treatment for obstructive sleep apnoea. Results of previous meta-analyses of randomised controlled trials showed continuous

***Panel:* Research in context**

Evidence before this study

Several previous meta-analyses have assessed the efficacy of continuous positive airway pressure and mandibular advancement devices on daytime sleepiness propensity as measured by the Epworth Sleepiness Scale (ESS) in patients with obstructive sleep apnoea. Findings of these studies have shown that both treatments were more effective in reducing ESS score compared with an inactive control (eg, placebo or no treatment); however, neither treatment was superior despite continuous positive airway pressure being more effective at reducing obstructive sleep apnoea severity. Because continuous positive airway pressure and mandibular advancement devices have only been directly compared in a few studies, meta-analyses may have not been powered to detect a true difference between these interventions. In subgroup analyses, the effect of continuous positive airway pressure compared with inactive controls seemed to be greater in trials of patients with more severe obstructive sleep apnoea or greater daytime sleepiness although differences between subgroups do not seem to have been formally tested. In particular, the effect of nightly continuous positive airway pressure usage on the reported effects of continuous positive airway pressure has not been investigated in meta-analyses so far, despite findings of previous trials showing associations between higher continuous positive airway pressure adherence and greater reductions in daytime sleepiness.

Added value of this study

In contrast to previous studies, we used a network meta-analysis to strengthen the comparison of continuous positive airway pressure and mandibular advancement devices on ESS score. This increasingly popular approach works by combining data from trials in which two treatments were directly compared with trials in which they were compared with other common treatments. When we incorporated data from the many trials in which continuous positive airway pressure or mandibular advancement devices were compared with inactive controls, we noted that continuous positive airway pressure seemed to be more effective than mandibular advancement devices in reducing ESS score. We also noted that both treatments were effective in reducing daytime sleepiness compared with an inactive control, thus supporting present evidence. In meta-regression analyses, we found that continuous positive airway pressure was likely to be more effective in reducing ESS score in patients with greater daytime sleepiness at baseline and, to a lower extent, in patients with more severe obstructive sleep apnoea. Surprisingly, trials reporting greater continuous positive airway pressure usage did not tend to also report larger effects of continuous positive airway pressure relative to an inactive control.

Implications of all the available evidence

Both continuous positive airway pressure and mandibular advancement devices are effective treatments for reducing daytime sleepiness. Continuous positive airway pressure seems to be the more effective treatment and should be the first-line treatment for obstructive sleep apnoea whereas mandibular advancement devices are an effective alternative treatment when patients cannot tolerate continuous positive airway pressure. Continuous positive airway pressure is probably most effective in patients with greater daytime sleepiness or more severe obstructive sleep apnoea; however, longer continuous positive airway pressure usage per night did not seem to be associated with a better outcome and requires further investigation.

positive airway pressure reduced ESS by more than 2 points compared with conservative management. Additionally, the effect seemed to be larger in trials of patients with more severe obstructive sleep apnoea or higher daytime sleepiness at baseline.[9,10] However, to our knowledge, the effect of continuous positive airway pressure compliance on ESS has not been assessed in meta-analyses despite previous trials[11–13] showing associations between higher continuous positive airway pressure adherence and greater reductions in daytime sleepiness.

Despite its effectiveness, continuous positive airway pressure treatment can sometimes not be tolerated by patients, mainly because of discomfort or nasal problems.[14] The main alternative treatment for such patients and a treatment commonly used in cases of milder obstructive sleep apnoea is a mandibular advancement device, which works by protruding the mandible during sleep to help prevent the airways from collapsing.[15] Findings of previous meta-analyses have also shown that mandibular advancement devices reduce ESS compared with conservative management, albeit to a slightly lower extent than continuous positive airway pressure.[10,16] However, when investigators did meta-analyses combining studies in which continuous positive airway pressure and mandibular advancement devices were directly compared, no difference was detected between the two treatments on ESS although continuous positive airway pressure was shown consistently to be more effective in reducing sleep apnoea severity.[9,10,16,17] In the most recent meta-analysis,[10] researchers noted a non-significant difference of 0·7 points in favour of continuous positive airway pressure compared with mandibular advancement devices; however, this analysis might have lacked sufficient power due to combining only ten studies in which the two treatments were directly compared.

In our meta-analysis, we undertook an updated systematic scientific literature search of randomised controlled trials comparing continuous positive airway pressure, mandibular advancement devices, or inactive controls (ie, placebo, no treatment or usual care) on ESS and combined the results of studies with a network meta-analysis.[18] This increasingly popular approach for

estimating differences between several treatments can combine data from trials in which two treatments were directly compared with trials in which they have been compared with other treatments. Therefore, this approach is useful for improving the comparison of treatments such as continuous positive airway pressure and mandibular advancement devices, which have been directly compared in a few studies. We also investigated how the reported effect of continuous positive airway pressure versus an inactive control varies over certain trial characteristics such as the average baseline obstructive sleep apnoea severity and sleepiness of participants. In particular, we aimed to establish how much continuous positive airway pressure usage is needed for a patient to benefit from a reduction in daytime sleepiness.

Methods

Inclusion criteria

To be deemed eligible, trials had to have recruited patients aged 18 years and older with a diagnosis of obstructive sleep apnoea defined by an apnoea–hypopnoea index (AHI) of five or more apnoea or hypopnoea episodes per hour and have randomly assigned them to any combination of continuous positive airway pressure (fixed or autotitrating), mandibular advancement device (fixed or adjustable), or an inactive control. Inactive controls were classed as sham continuous positive airway pressure, placebo mandibular advancement device, any other type of placebo (eg, placebo tablet), no treatment, or usual or standard care. Randomised controlled trials of patients with a concurrent disease (eg, heart failure and stroke) were eligible for inclusion. To be included in the meta-analysis, trials had to have measured ESS scores at baseline and a follow-up visit and reported with some measure of variability (eg, standard deviation or error) either the average ESS score at each visit, the average change in each group at follow-up compared with baseline, or a treatment effect for the difference in the change in ESS score between groups. Both parallel and crossover randomised controlled trials and only trial reports or conference abstracts published in English were eligible. We did not include substudies in the meta-analysis unless insufficient data were reported in the larger, main trial. The appendix provides the protocol for the meta-analysis.

Identification of trials

We searched MEDLINE and the Cochrane Library from inception to May 31, 2015, using the Cochrane Highly Sensitive Search Strategy (sensitivity-maximising and precision-maximising version) for identifying randomised controlled trials.[19] The appendix provides a list of the search terms used for each electronic database. We screened bibliographies of all eligible trial reports and any relevant review papers for further potentially eligible trials.

Selection of studies and data extraction

DJB did the literature search and the eligibility of studies was determined by DJB, TG, and CS. DJB extracted the relevant data from eligible studies, which were then independently checked for accuracy by TG and CS. The following trial characteristics were extracted from each study: year of publication, trial design (parallel or crossover), inclusion criteria, type of treatment groups assessed, sample size, number analysed, and length of follow-up. Mean baseline ESS, AHI, oxygen desaturation index, age, body-mass index (BMI), continuous positive airway pressure usage (h per night), and proportion of male participants were also recorded.

The treatment effect of interest was the absolute mean difference between groups in the change in the ESS scores from baseline to follow-up. If possible, this was directly extracted from studies along with the corresponding standard error, confidence interval (CI), or p value. Treatment effects that were adjusted for prognostic factors (eg, baseline ESS score) were preferable. If a treatment effect was not reported then we recorded the mean (SD) change in ESS over follow-up in each group or the mean (SD) ESS score for each group at each visit. If ESS data from several visits were reported, data from the latest available follow-up visit was used in the analysis. Only data presented in published articles were used and study authors were not contacted for missing information because of time constraints and because such data cannot be verified by readers.

Endpoints

The primary outcome of the meta-analysis was the absolute change in ESS score from baseline to follow-up in each of the following treatment comparisons: continuous positive airway pressure versus inactive control; mandibular advancement device versus inactive control; and continuous positive airway pressure versus mandibular advancement device.

In the comparison of continuous positive airway pressure to inactive controls, we also investigated the association between the mean reported continuous positive airway pressure usage (measured in h per night) and the treatment effect on ESS scores to establish whether trials with greater continuous positive airway pressure usage also reported a larger reduction in ESS score. In exploratory analyses, we similarly investigated the association between the reported treatment effect and the mean baseline ESS score, AHI, oxygen desaturation index, age, BMI, neck circumference, length of follow-up, and type of control group (sham continuous positive airway pressure, no treatment, or other type of placebo).

See Online for appendix

Risk of bias assessment

DJB, TG, and CS assessed the studies included in the meta-analyses for their risk of bias using the Cochrane

Collaboration's tool for assessing risk of bias.[20] Using this instrument, each study was assessed on several types of bias (selection, performance, detection, attrition, and reporting bias) and categorised as being at low, unclear, or high risk of bias in each domain. The reported treatment effects of studies at low and high risk in each domain were then compared assuming that all studies at unclear risk of bias were either at low or high risk in separate analyses.

Statistical methods

In studies reporting only the average ESS score at each visit, an estimate of the correlation between ESS score at baseline and follow-up is needed to calculate the standard error (SE) of the treatment effect. This figure was obtained by first calculating the correlation in studies reporting the necessary information using the methods described in section 16.1.3.2 of the Cochrane handbook.[21] We then used the mean correlation from these to impute the standard errors of the treatment effects in other studies, with the limits of the 95% CI of the mean being used in sensitivity analyses. In crossover studies not reporting a treatment effect from an analysis specific to paired data, the between-period correlation was assumed to be zero; this is a reasonable assumption when changes from baseline are of interest.[22]

We used multivariate random-effects meta-regression using the network family of commands in Stata (version 14.0) for the network meta-analysis.[23] We fitted a consistency model, which assumes that treatment effects from direct and indirect comparisons are in agreement. An unstructured between-study covariance matrix was used to allow for the possibility of unequal levels of heterogeneity in the different comparisons. To test for inconsistency, we added design-by-treatment interactions to the consistency model where design refers to the set of treatments in a trial.[23] To further investigate the plausibility of the consistency assumption, we compared trial characteristics across the different designs. Comparison-adjusted funnel plots were used to assess small study effects.

To work out whether direct evidence alone differed from the findings of the network meta-analysis, we did separate pairwise meta-analyses of direct evidence only for each treatment comparison with the metan command in Stata.[24] In each analysis heterogeneity was assessed using the between-study variance (τ^2), Cochran's Q test, and the I^2 statistic.[25] Only random-effects models were used to be consistent with the network meta-analysis. Forest plots were used to summarise study-level and pooled treatment effects. If evidence of inconsistency was found in the network meta-analysis, then we drew conclusions from the pairwise analyses.

We used meta-regression to assess the association between trial characteristics and the reported effects of

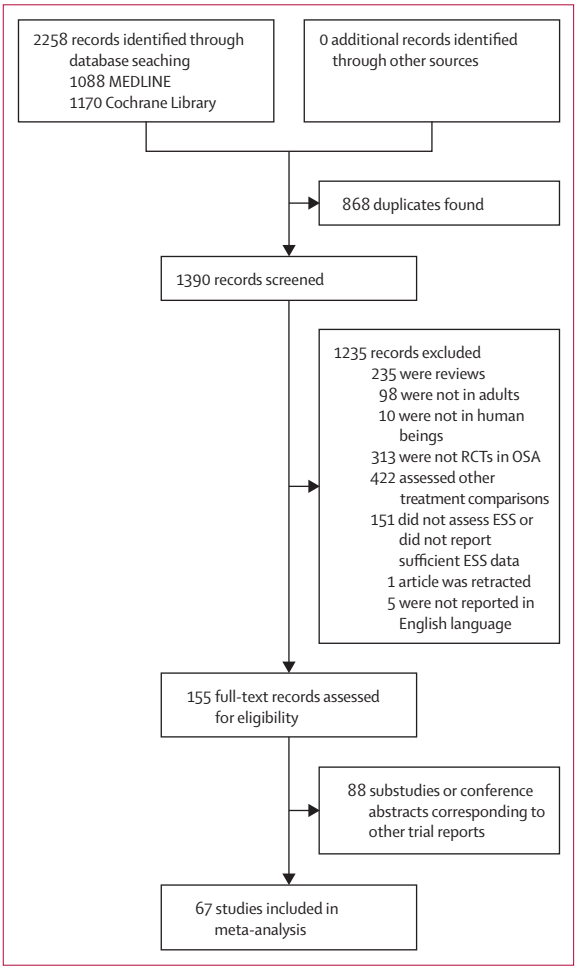

Figure 1: **PRISMA flow diagram**
RCT=randomised controlled trial. OSA=obstructive sleep apnoea. ESS=Epworth Sleepiness Scale.

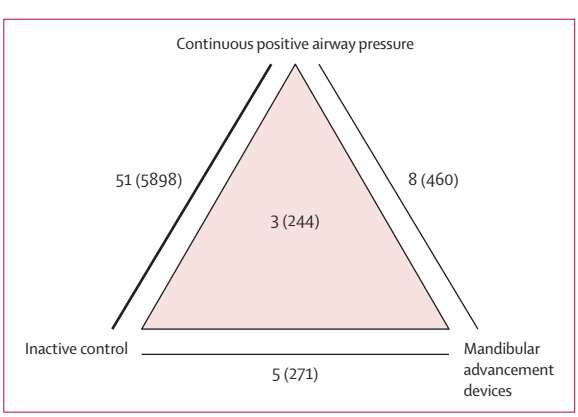

Figure 2: **Network map showing the number of trials in which continuous positive airway pressure, mandibular advancement devices, and inactive controls are compared and the total sample size in each comparison in parentheses**
The middle triangle represents the number of studies in which all three interventions were directly compared.

continuous positive airway pressure versus inactive control using the metareg command in Stata.[26] We also used meta-regression to compare pooled treatment effects of studies at low or high risk of bias in each domain of the Cochrane Collaboration's method.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and co-authors had full access to the data in the study and take responsibility for the integrity of the data, the accuracy of the analyses, and the decision to submit for publication.

Results

We included 67 eligible studies[11–13,27–90] comprising 6873 patients in the analysis (figure 1, appendix). 51 of these studies (5898 patients) assessed continuous positive airway pressure against an inactive control only (figure 2). Eight studies (460 patients) compared continuous positive airway pressure with a mandibular advancement device, five (271 patients) assessed a mandibular advancement device against an inactive control, and three (244 patients) directly compared all three interventions. The appendix summarises trial characteristics for each type of treatment comparison. There was some evidence that the mean BMI varied across comparisons although the differences between the means were small. Importantly, the mean baseline ESS score was similar across comparisons and thus we felt that the consistency assumption of the network meta-analysis was not likely to be incorrect in this regard.

The table shows the results of the pairwise and network meta-analyses.We noted no inconsistency in the network meta-analysis and so we drew the main conclusions from the consistency model. Compared with inactive controls, continuous positive airway pressure and mandibular advancement devices were estimated to reduce ESS score by 2·5 (95% CI 2·0–2·9) and 1·7 (95% CI 1·1–2·3) points, respectively (both p<0·0001). Continuous positive airway pressure was estimated to reduce ESS by an additional 0·8 points (95% CI 0·1–1·4; p=0·015) compared with mandibular advancement devices. The results of the pairwise meta-analyses (table, figure 3, appendix) combining direct evidence only for each treatment comparison were very similar to those of the network meta-analysis, albeit with wider confidence intervals probably because less information was included.

The mean estimated correlation between ESS scores at baseline and follow-up in studies reporting sufficient ESS data (n=9) was 0·53 (95% CI 0·36–0·69). A sensitivity analysis using the limits of the confidence interval rather than the mean to impute missing standard errors did not greatly alter the results of the network meta-analysis (appendix). One included study was reported as a conference abstract[74] and excluding it did not change any findings.

There was no indication that studies reporting higher continuous positive airway pressure usage also reported larger effects of continuous positive airway pressure on ESS (p=0·70; figure 4). This was also the case when only considering studies that used sham continuous positive airway pressure as a control (data not shown). There was strong evidence that the effect of continuous positive airway pressure was greater in studies of sleepier patients (ie, larger mean baseline ESS; p=0·003; appendix) and similar but less pronounced trends were recorded for AHI (p=0·051), oxygen desaturation index (p=0·022), and BMI (p=0·066;

	Treatment effect (SE)	95% CI	p value	Cochran's Q test, p value	I^2 statistic	Between-study variance (τ^2)
Continuous positive airway pressure *vs* control						
Pairwise	−2·4 (0·2)	−2·8 to -2·0	<0·0001	<0·0001	74%	1·40
Network	−2·5 (0·2)	−2·9 to -2·0	<0·0001	..	..	1·87
Mandibular advancement devices *vs* control						
Pairwise	−1·7 (0·4)	−2·5 to -1·0	<0·0001	0·29	17%	0·18
Network	−1·7 (0·3)	−2·3 to -1·1	<0·0001	..	..	0·08
Continuous positive airway pressure *vs* mandibular advancement devices						
Pairwise	−0·9 (0·5)	−1·8 to 0·0	0·060	0·001	67%	1·38
Network	−0·8 (0·3)	−1·4 to −0·1	0·015	..	..	1·19

Test for inconsistency in network meta-analysis: $\chi^2(3)=4·4$; p=0·22.

Table: **Results of pairwise and network meta-analyses comparing continuous positive airway pressure, mandibular advancement devices, and inactive controls on Epworth Sleepiness Scale score**

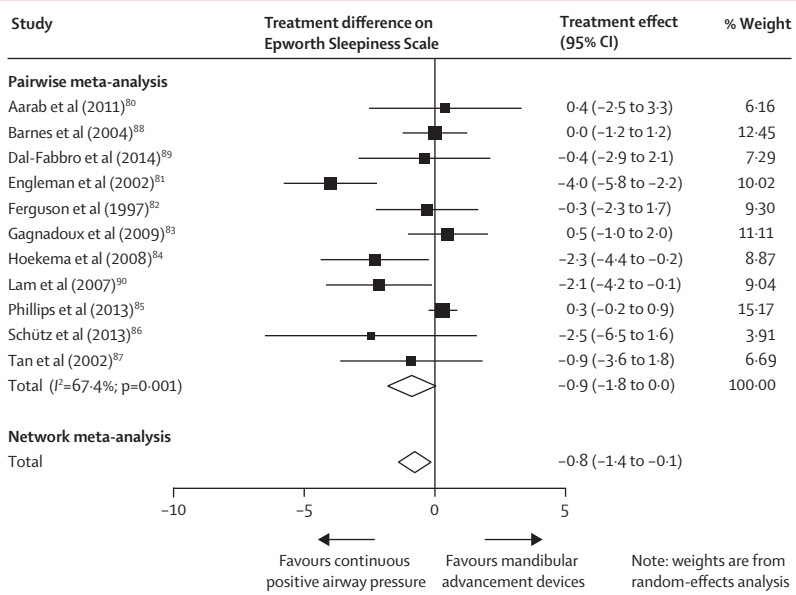

Figure 3: **Forest plot showing the results of studies directly comparing the effects of continuous positive airway pressure to mandibular advancement devices on ESS scores and the pooled effects estimated in the pairwise and network meta-analyses**

Box sizes are proportional to the weight of the corresponding study in the pairwise random-effects meta-analysis.

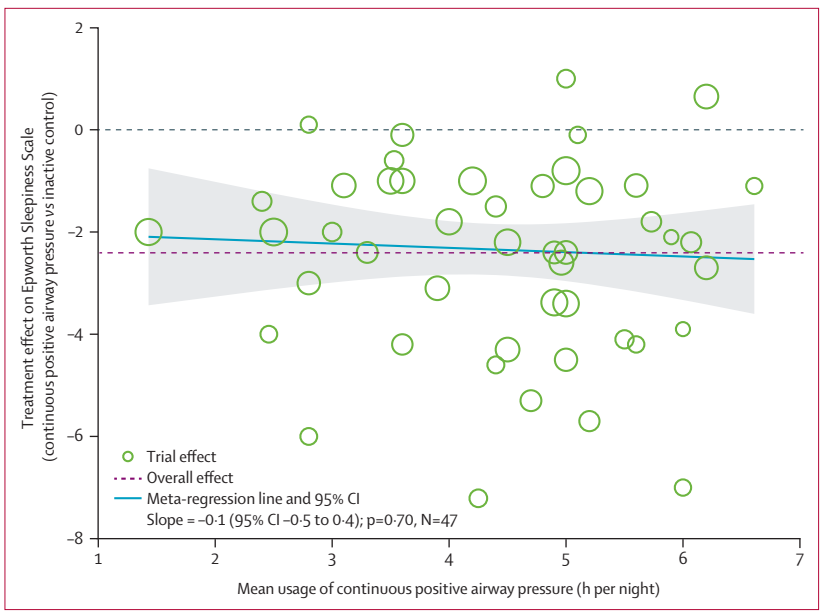

Figure 4: **Association between mean continuous positive airway pressure usage and the reported treatment effect on ESS scores in studies comparing continuous positive airway pressure to an inactive control**
Circles represent individual studies. The size of each circle is proportional to the weight of the corresponding study in the pairwise random-effects meta-analysis.

appendix). There was no evidence that trials of shorter duration or of patients with a higher mean age reported larger treatment effects (appendix), nor that the effect of continuous positive airway pressure differed between trials using different types of control group (appendix).

We recorded some suggestion that smaller studies tended to report larger treatment effects in favour of continuous positive airway pressure when compared with mandibular advancement devices or inactive controls (appendix). There was a weak correlation between sample size and mean baseline ESS score (r=–0·19), which, in view of the fact that trials of sleepier patients tended to report larger effects of continuous positive airway pressure, might partly explain these small study effects. However, we cannot eliminate the possibility of publication bias. Therefore to limit the effect of smaller trials, we did a post-hoc fixed-effects network meta-analysis. In this analysis the estimated effect of continuous positive airway pressure was slightly smaller than that in the random-effects model and more similar to the effect of mandibular advancement devices (difference=–0·2, 95% CI –0·5 to 0·2; p=0·36; appendix).

The appendix shows the proportion of trials at low, unclear, and high risk of bias in each domain of the Cochrane Collaborations' risk of bias instrument. The risk of selection bias was unclear in most studies because they did not adequately describe their methods of randomisation and allocation concealment. Additionally, most studies were deemed to be at high risk of performance and detection bias because they compared treatments that could not be masked (eg, continuous positive airway pressure *vs* no treatment or mandibular advancement devices). There was evidence that the effect of continuous positive airway pressure versus inactive controls differed in studies at high risk of selection bias compared with those at low risk due to poor allocation concealment (appendix), although the number of such studies was small (n=7/54) and the bias was in favour of control rather than continuous positive airway pressure.

Discussion

To our knowledge, this is the first network meta-analysis to investigate the effects of continuous positive airway pressure and mandibular advancement devices on daytime sleepiness in patients with obstructive sleep apnoea. Continuous positive airway pressure and mandibular advancement devices were associated with reductions in daytime sleepiness, as measured by ESS, of 2·5 and 1·7 points, respectively, compared with control, which will probably translate into improvements in quality of life, work productivity,[3] and reductions in sleep-related road accidents.[4] Additionally, we noted a significant difference of 0·8 ESS points in favour of continuous positive airway pressure compared with mandibular advancement devices. This finding is not consistent with previous meta-analyses that might have lacked power by only combining studies in which continuous positive airway pressure and mandibular advancement devices were directly compared.[10,16,17] An advantage of our network meta-analysis is that it also incorporates results from trials in which the two active treatments were not directly compared, which in this case led to more precise treatment effect estimates (table).

We noted that trials of patients who were sleepier at baseline and, to a lesser extent, who had more severe obstructive sleep apnoea tended to report larger effects of continuous positive airway pressure compared with controls. This result might explain partly why the effect of continuous positive airway pressure was greater than mandibular advancement devices because patients in trials of continuous positive airway pressure versus inactive control had a higher mean AHI than those in trials of mandibular advancement devices (perhaps because of the differing scenarios in which each treatment is used in practice). However, when incorporating this indirect evidence into the comparison of continuous positive airway pressure and mandibular advancement devices in the network meta-analysis, the difference between the two treatments was not inflated compared with when only direct evidence was studied—ie, when patient characteristics were similar between treatment groups. Therefore, because the results of all treatment comparisons were consistent, we do not believe that any differences in AHI between comparisons significantly affected our results. Baseline ESS score was a stronger effect modifier

for continuous positive airway pressure, and this variable was similar in each comparison.

We did not find that trials reporting higher average usage of continuous positive airway pressure also reported larger differences between continuous positive airway pressure and inactive controls. Thus, it seems that any amount of continuous positive airway pressure usage is equally beneficial, which is in contrast to a previous network meta-analysis showing that at least 3 h per night are probably needed to reduce systolic and diastolic blood pressure.[91] This result is surprising in view of the fact that several randomised controlled trials included in this meta-analysis have reported an association between higher continuous positive airway pressure usage and reduced sleepiness.[12,13,36,61] Our finding could have been the consequence of detection bias because many studies could not mask patients to treatment allocation. However, no association was also recorded when we only included those trials in which patients could be masked through the use of sham continuous positive airway pressure as a control. Another possibility is that the associations estimated between treatment effect and average patient characteristics might not be the same as those that would have been estimated more accurately using individual patient data.[92] For instance, a recent individual patient data meta-analysis of four trials investigating the effect of continuous positive airway pressure in patients with minimally symptomatic obstructive sleep apnoea noted that the reduction in ESS scores was greater in patients using continuous positive airway pressure for more than 4 h per night compared with those using it for less than 4 h per night.[93] Therefore, acquisition of individual patient data for the trials included in this study is necessary to investigate the associations more accurately, but would prove challenging due to the large number of studies involved. Alternatively the effect of continuous positive airway pressure usage could be investigated in a dose–response trial in which patients with obstructive sleep apnoea are randomly assigned to various durations of continuous positive airway pressure per night, although this is likely to face various challenges including a large sample size requirement and difficulties in maintaining masking.

There was some suggestion that smaller studies tended to report larger treatment effects in favour of continuous positive airway pressure. This finding might be explained partly by the characteristics of smaller studies, but could also be the result of publication bias. Results of a fixed-effects network meta-analysis that limited the effect of smaller studies showed a slightly lower effect of continuous positive airway pressure on ESS score compared with inactive controls and also a smaller and statistically non-significant difference between continuous positive airway pressure and mandibular advancement devices. However, such an analysis is arguably inappropriate in this situation because of the large amount of heterogeneity (table).

We did not study other treatments for obstructive sleep apnoea such as weight loss and positional treatment because of the small number of trials comparing these treatments with each other and with continuous positive airway pressure and mandibular advancement devices. Furthermore, inclusion of these treatments might have led to modelling difficulties when estimating the between-trial variance of treatments that were not directly compared. Nonetheless, because continuous positive airway pressure is the first-line treatment for most patients with obstructive sleep apnoea and mandibular advancement devices are a commonly used treatment for milder cases of obstructive sleep apnoea or more severe patients unable to tolerate continuous positive airway pressure,[15] we believed that these two treatments would be of greatest interest to clinicians. Future network meta-analyses could incorporate other obstructive sleep apnoea treatments, which would also allow for the comparison of treatments that themselves have not been directly compared.[18]

In conclusion, our findings support existing evidence that continuous positive airway pressure and mandibular advancement devices are effective at reducing subjective daytime sleepiness as measured by the ESS score. However, in contrast to previous meta-analyses, our data suggest that continuous positive airway pressure is more effective than mandibular advancement devices at reducing daytime sleepiness. Nonetheless, mandibular advancement devices should remain a suitable alternative treatment when continuous positive airway pressure is not tolerable. The meta-regression analyses showed that the effects of continuous positive airway pressure treatment are likely to be greatest in patients with more severe or more symptomatic obstructive sleep apnoea although milder cases will also benefit. Of note, longer continuous positive airway pressure usage per night was not associated with a better outcome and this requires further investigation.

Contributors

DJB and MK conceived and designed the study. DJB reviewed the scientific literature, did the statistical analysis, prepared all tables and figures, and wrote the first draft of the report. DJB, TG, and CS contributed to acquisition of data and quality assessment.

Declaration of interests

MK reports grants from Swiss National Science Foundation and grants from University of Zurich during the conduct of the study. The other authors declare no competing interests.

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Original Investigation

CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea
A Systematic Review and Meta-analysis

Daniel J. Bratton, PhD; Thomas Gaisl, MD; Annette M. Wons, MD; Malcolm Kohler, MD

IMPORTANCE Obstructive sleep apnea is associated with higher levels of blood pressure (BP), which can lead to increased cardiovascular risk.

OBJECTIVE To compare the association of continuous positive airway pressure (CPAP), mandibular advancement devices (MADs), and inactive control groups (placebo or no treatment) with changes in systolic BP (SBP) and diastolic BP (DBP) in patients with obstructive sleep apnea.

DATA SOURCES The databases of MEDLINE, EMBASE, and the Cochrane Library were searched up to the end of August 2015 and study bibliographies were reviewed.

STUDY SELECTION Randomized clinical trials comparing the effect of CPAP or MADs (vs each other or an inactive control) on BP in patients with obstructive sleep apnea were selected by consensus. Of 872 studies initially identified, 51 were selected for analysis.

DATA EXTRACTION AND SYNTHESIS Data were extracted by one reviewer and checked by another reviewer. A network meta-analysis using multivariate random-effects meta-regression was used to estimate pooled differences between each intervention. Meta-regression was used to assess the association between trial characteristics and the reported effects of CPAP vs inactive control.

MAIN OUTCOMES AND MEASURES Absolute change in SBP and DBP from baseline to follow-up.

RESULTS Of the 51 studies included in the analysis (4888 patients), 44 compared CPAP with an inactive control, 3 compared MADs with an inactive control, 1 compared CPAP with an MAD, and 3 compared CPAP, MADs, and an inactive control. Compared with an inactive control, CPAP was associated with a reduction in SBP of 2.5 mm Hg (95% CI, 1.5 to 3.5 mm Hg; $P < .001$) and in DBP of 2.0 mm Hg (95% CI, 1.3 to 2.7 mm Hg; $P < .001$). A 1-hour-per-night increase in mean CPAP use was associated with an additional reduction in SBP of 1.5 mm Hg (95% CI, 0.8 to 2.3 mm Hg; $P < .001$) and an additional reduction in DBP of 0.9 mm Hg (95% CI, 0.3 to 1.4 mm Hg; $P = .001$). Compared with an inactive control, MADs were associated with a reduction in SBP of 2.1 mm Hg (95% CI, 0.8 to 3.4 mm Hg; $P = .002$) and in DBP of 1.9 mm Hg (95% CI, 0.5 to 3.2 mm Hg; $P = .008$). There was no significant difference between CPAP and MADs in their association with change in SBP (−0.5 mm Hg [95% CI, −2.0 to 1.0 mm Hg]; $P = .55$) or in DBP (−0.2 mm Hg [95% CI, −1.6 to 1.3 mm Hg]; $P = .82$).

CONCLUSIONS AND RELEVANCE Among patients with obstructive sleep apnea, both CPAP and MADs were associated with reductions in BP. Network meta-analysis did not identify a statistically significant difference between the BP outcomes associated with these therapies.

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Author Affiliations: Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland (Bratton, Gaisl, Wons, Kohler); Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland (Kohler); Center for Interdisciplinary Sleep Research, University of Zurich, Zurich, Switzerland (Kohler).

Corresponding Author: Malcolm Kohler, MD, University Hospital Zürich, Rämistrasse 100, 8091 Zürich, Switzerland (malcolm.kohler@usz.ch).

Obstructive sleep apnea is characterized by recurring cessations or reductions in respiratory flow due to upper airway collapse during sleep. The estimated prevalence of symptomatic obstructive sleep apnea in Western countries is 2% to 4%; however, prevalence is increasing due to levels of obesity in these populations.[1] The condition is associated with oxygen desaturations and arousals from sleep, which can lead to increases in blood pressure (BP) and risk of cardiovascular disease.[2]

Continuous positive airway pressure (CPAP) has been shown to be an effective treatment for improving symptoms of obstructive sleep apnea, such as daytime sleepiness,[3] and meta-analyses have shown it to be associated with a reduction of about 2 mm Hg in BP.[4-8] However, the estimated association of trial-level characteristics (mean nightly CPAP use in particular) with the effects of CPAP reported in individual randomized clinical trials (RCTs) has been less consistent.[5,6]

Alternative treatments often used by patients unable to tolerate CPAP are mandibular advancement devices (MADs), which work by protruding the mandible and tongue to keep airways open during sleep.[9] The association of use of MADs with reductions in BP is less clear. A recent meta-analysis that included only 2 RCTs was inconclusive.[10] To our knowledge, no meta-analysis has comprehensively compared CPAP vs MADs on change in BP, perhaps due to a lack of RCTs. The most recent meta-analysis[5] briefly reviewed 2 trials,[11,12] comparing the effects of CPAP with MADs on change in BP, and found conflicting results between the studies.

The primary aim of our study was to perform a network meta-analysis[13] comparing the association of CPAP vs MADs and vs an inactive control (eg, placebo or no treatment) with changes in systolic BP (SBP) and diastolic BP (DBP) in patients with obstructive sleep apnea. A secondary aim was to explore the association of trial-level characteristics, such as mean nightly CPAP use, with the reported treatment effects of CPAP vs inactive control therapy on BP outcomes.

Methods

Inclusion Criteria

The studies must have randomized participants aged 18 years or older with a diagnosis of obstructive sleep apnea (defined by an apnea-hypopnea index of ≥5/h) to at least 2 of the following treatments: (1) CPAP, (2) MADs, or (3) inactive control, such as sham CPAP, placebo MADs, or conservative treatment (no active therapy). Trials must also have measured and reported data on SBP or DBP at a follow-up visit and preferably also at enrollment or randomization, or reported a treatment effect for either outcome. If 2 eligible studies contained a significant overlap in patients, the larger of the 2 studies was used in the analysis. The protocol for this meta-analysis appears in Supplement 1.

Identification of Trials

Literature searches were performed independently by 2 of the authors (D.J.B. and A.M.W.) using the databases of MEDLINE, EMBASE, and the Cochrane Library from inception to the end of August 2015. The RCTs were identified using the Cochrane Collaboration highly sensitive search strategy (sensitivity-maximizing and precision-maximizing version).[14] The general electronic search strategy appears in Supplement 2. The bibliographies of all eligible trials and review articles were also screened for relevant trials that might have been missed in the database search. Inclusion was restricted to trials reported in English.

Selection of Studies and Data Extraction

Two of the authors (D.J.B. and A.M.W.) assessed the eligibility of studies found in the literature searches. One author (D.J.B.) extracted the relevant data from eligible studies, which was then independently checked by another author (T.G.). Trial characteristics, such as sample size, length of follow-up, type of control group (eg, placebo or no treatment), and type of study (eg, crossover or parallel), were recorded. The main outcome of interest was the change in SBP and DBP between baseline and follow-up in the 3 treatment groups (CPAP, MADs, inactive control). Treatment effects were extracted directly from the studies along with standard errors, 95% confidence intervals, or *P* values. If treatment effects were not reported, other data, such as mean (standard deviation) for SBP and DBP for each treatment group at each visit or the change in SBP and DBP between visits in each group, were recorded and used to estimate the treatment effect of interest.

Measurements of BP during the daytime (while the patient was ambulatory), during the morning, or during an office visit were preferable (in that order). Otherwise, 24-hour ambulatory BP measurements were used. Summary statistics for the following baseline data were also recorded: age, body mass index (calculated as weight in kilograms divided by height in meters squared), apnea-hypopnea index, oxygen desaturation index, Epworth Sleepiness Scale score, and proportion of male participants. We also extracted the mean nightly use of CPAP from trials comparing CPAP with an inactive control.

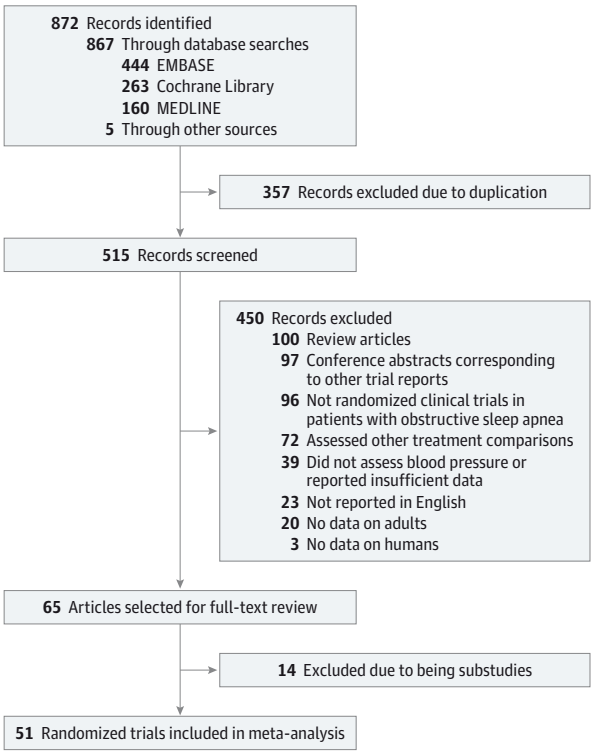
End Points

The primary outcomes were the absolute changes in SBP and DBP from baseline to follow-up in each of the following treatment comparisons: (1) CPAP vs inactive control, (2) MADs vs inactive control, and (3) CPAP vs MADs. For the first comparison (CPAP vs inactive control), we also investigated the association of mean CPAP use with the treatment effects reported in each trial for both outcomes of SBP and DBP. We also explored the association between the reported treatment effects and mean baseline apnea-hypopnea index, oxygen-desaturation index, baseline BP, length of follow-up, type of control group (sham CPAP, no treatment, or other placebo), and type of BP measurement (daytime, morning, office, or 24 hour). Similar investigations for the second and third comparisons were not made due to the insufficient number of studies directly comparing these treatments.

Risk of Bias Assessment

Two authors (D.J.B. and T.G.) evaluated the risk of bias in each study included in the meta-analysis using the Cochrane

Figure 1. Flowchart of Literature Search and Study Selection



Collaboration tool for assessing risk of bias.[15] This tool assesses studies on different sources of bias (selection, detection, performance, attrition, or reporting bias) and categorizes studies by low, unclear, or high risk of bias in each domain. We then planned to compare the reported treatment effects on SBP and DBP in studies at low and high risk of bias in each domain using meta-regression.

Statistical Methods

If treatment effects or changes in SBP and DBP in each treatment group were not reported in studies, then the mean (standard deviation) values for each outcome, in each group, and at each visit were extracted and used to estimate treatment effects. To calculate standard error, an estimate of the correlation between SBP and DBP measurements at baseline and follow-up was required. Previous meta-analyses[6,7] have assumed this correlation to be 0.5, which might not be appropriate. We instead estimated the correlation in all studies for which it was possible (ie, those reporting standard deviations or standard errors of treatment effects or changes during follow-up and the standard deviations at each visit) and used the mean correlation to impute the treatment effect standard error in studies for which estimation was not possible. To assess the sensitivity of our results to this correlation, we repeated the meta-analysis using the minimum and maximum correlations estimated from the studies. In crossover studies not reporting treatment effects from paired *t* tests (or tests accounting for the between-period correlation), the between-period correlation was assumed to be zero, slightly increasing the conservatism of the analysis.[16] In studies not reporting data on baseline BP, conservative estimates of treatment effects were obtained by estimating the differences between treatment groups in follow-up BP measurements.

Separate meta-analyses of direct evidence only (pairwise meta-analyses) were conducted for each of the 3 treatment comparisons listed above using the metan command in Stata version 14.0 (StataCorp).[17] Heterogeneity was assessed using the estimated between-study variance (τ^2), Cochran χ^2 test, and the I^2 statistic.[18] Only random-effects models were used to be consistent with the network meta-analysis. To assess the association of trial characteristics and risk of bias with the reported effects of CPAP compared with an inactive control, we used random-effects meta-regression (metareg command in Stata[19]), and only included studies directly comparing these 2 interventions. To be consistent with the pairwise random-effects meta-analyses, we performed each meta-regression without the use of the adjustment method by Knapp and Hartung,[20] but also applied the adjustment in a sensitivity analysis.

Because there are relatively few trials directly comparing CPAP vs MADs on change in BP, a meta-analysis of only direct evidence is likely to lack power. To strengthen this and all other treatment comparisons, we performed a network meta-analysis. Unlike traditional meta-analyses, this method has the advantage of allowing trials comparing CPAP or MADs with some other common treatment (eg, placebo) to be incorporated into the analysis, thus increasing power and enabling a better comparison of CPAP and MADs to be made.[13]

We used multivariate, random-effects meta-regressions to perform each analysis using the network family of commands in Stata.[21] We first fitted a consistency model, which assumes that treatment effects from direct and indirect comparisons are in agreement. An unstructured between-study covariance matrix was used to allow for the possibility of unequal levels of heterogeneity in each comparison. We also performed a sensitivity analysis for which heterogeneity was assumed to be the same in each comparison. To test for inconsistency, design × treatment interactions were added to the consistency model, in which design refers only to the set of treatments in a trial (4 sets in total). To further investigate the plausibility of the consistency assumption, we also checked whether potential effect modifiers were similar across different designs.[22] If inconsistency was not rejected, we estimated the probability of each treatment having the strongest association with BP reduction by applying the parametric bootstrap procedure (with 5000 draws), which was described by White.[23] Forest plots were used to summarize study level and pooled treatment comparisons and comparison-adjusted funnel plots were used to assess publication bias.[24] All analyses were conducted at the 2-sided significance level of .05.

Results

A total of 51 eligible studies (4888 patients) were identified and included in the network meta-analysis (**Figure 1**). Of these 51

Table 1. Baseline Characteristics of Included Trials of Continuous Positive Airway Pressure (CPAP) vs Inactive Control

Source	Main Inclusion Criteria	Type of Design	Type of Control Therapy	Sample Size	Length of Follow-up, wk	Mean Age, y	Male Sex, %	Mean BMI[a]	Mean AHI, /h	ESS Score[b]	Time or Location of BP Measurement	Mean Baseline BP, mm Hg	
												Systolic	Diastolic
Arias et al,[25] 2005	AHI ≥10/h and ESS score ≥10	Crossover	Sham CPAP	27	12	52	100	31	44	NA	Daytime	127	79
Barbé et al,[26] 2001	AHI ≥30/h and ESS score ≤10	Parallel	Sham CPAP	55	6	53	91	29	55	7	Daytime	129	81
Barbé et al,[27] 2012	AHI ≥20/h and ESS score ≤10	Parallel	No placebo	725	26	52	86	31	38	7	Office	131	80
Barnes et al,[28] 2002	AHI 5-30/h	Crossover	Oral placebo	42	8	46	86	31	13	11	Daytime	132	84
Becker et al,[29] 2003	AHI ≥5/h and ESS score ≥10	Parallel	Sham CPAP	60	9	53	91	33	64	14	Daytime	141	86
Campos-Rodriguez et al,[30] 2006	Systemic arterial hypertension and AHI ≥10/h	Parallel	Sham CPAP	72	4	57	60	35	59	14	24 h	132	78
Comondore et al,[31] 2009	Minimal daytime sleepiness and AHI ≥15/h	Crossover	No placebo	13	4	56	69	31	28	7	24 h	138	84
Coughlin et al,[32] 2007	AHI >15/h and ESS score ≥10	Crossover	Sham CPAP	35	6	49	100	36	40[c]	14	Morning	NA	NA
Craig et al,[33] 2012	Insufficient daytime symptoms for CPAP and ODI >7.5 dips/h	Parallel	No placebo	391	26	58	78	32	13[d]	8	Daytime	130	81
Cross et al,[34] 2008	AHI >15/h and ESS score >10	Crossover	Sham CPAP	29	6	48	96	37	63	NA	Office	143	80
de Oliveira et al,[35] 2014	Resistant hypertension and AHI >15/h	Parallel	Sham CPAP	47	8	59	57	30	20	10	Daytime	150	90
Drager et al,[36] 2007	Male sex and AHI >30/h	Parallel	No placebo	24	17	46	100	30	59	14	Daytime	123	79
Drager et al,[37] 2011	Prehypertension or masked hypertension and AHI >30/h	Parallel	No placebo	36	13	43	100	29	56	12	Daytime	127	83
Durán-Cantolla et al,[38] 2010	Hypertension and AHI >15/h	Parallel	Sham CPAP	340	12	52	81	32	44	10	Daytime	134	86
Egea et al,[39] 2008	Chronic heart failure, AHI >10/h, and LVEF ≤45%	Parallel	Sham CPAP	73	13	63	93	31	42	8	NA	124	76
Engleman et al,[40] 1996	AHI ≥5/h and ≥2 OSA symptoms	Crossover	Oral placebo	13	3	51	85	36	49	NA	Daytime	NA	NA
Faccenda et al,[41] 2001	Two major symptoms of OSA and AHI ≥15/h	Crossover	Oral placebo	71	4	50	81	30	35	15	24 h	NA	NA
Gottlieb et al,[42] 2014	Berlin questionnaire score of 2-3, chronic heart disease or multiple cardiovascular risk factors, and AHI ≥15/h	Parallel	No placebo	212	12	63	77	33	25	8	Daytime	128	73
Hall et al,[43] 2014	Dyspnea, AHI >10/h, and LVEF ≤45%	Parallel	No placebo	45	7	62	76	NA	27	10	Office	118	NA
Hoyos et al,[44] 2012	Male sex, AHI ≥20/h, and ODI >15 dips/h	Parallel	Sham CPAP	65	12	49	100	31	40	10	Office	NA	NA
Hoyos et al,[45] 2015	AHI ≥25/h and ODI ≥20 dips/h	Crossover	Sham CPAP	38	8	49	87	31	40	11	Morning	126	77
Huang et al,[46] 2015	Hypertension, chronic heart disease, and AHI ≥15/h	Parallel	No placebo	83	157	62	82	28	29	9	Morning	147	83
Hui et al,[47] 2006	OSA-related symptoms and AHI ≥5/h	Parallel	Sham CPAP	56	13	51	77	27	31	11	Daytime	128	84
Ip et al,[48] 2004	Male sex and AHI ≥15/h	Parallel	No placebo	28	4	43	100	29	46	11	Morning	123	76

(continued)

Table 1. Baseline Characteristics of Included Trials of Continuous Positive Airway Pressure (CPAP) vs Inactive Control (continued)

Source	Main Inclusion Criteria	Type of Design	Type of Control Therapy	Sample Size	Length of Follow-up, wk	Mean Age, y	Male Sex, %	Mean BMI[a]	Mean AHI, /h	ESS Score[b]	Time or Location of BP Measurement	Mean Baseline BP, mm Hg	
												Systolic	Diastolic
Jones et al,[49] 2013	AHI ≥15/h	Crossover	Sham CPAP	53	12	46	58	30	31	13	Office	128	76
Kohler et al,[50] 2011	CPAP use >4 h/night during past year and ODI >10 dips/h off CPAP	Parallel	Sham CPAP	41	2	63	98	33	41	15	Morning	131	82
Lam et al,[51] 2010	Male sex and AHI ≥15/h	Parallel	Sham CPAP	61	1	46	100	28	32	11	Morning	130	81
Litvin et al,[52] 2013	Hypertension and AHI >30/h	Crossover	Sham CPAP	44	3	56	77	38	63	NA	Office	141	85
Lozano et al,[53] 2010	Resistant hypertension and AHI ≥15/h	Parallel	No placebo	75	13	59	69	31	53	6	Daytime	133	78
Martínez-García et al,[54] 2013	Resistant hypertension and AHI ≥15/h	Parallel	No placebo	194	12	56	69	34	40	9	Daytime	146	85
McMillan et al,[55] 2014	Age ≥65 y, ESS score ≥9, and ODI >7.5 dips/h	Parallel	No placebo	278	52	71	82	34	29[d]	12	Office	140	78
Monasterio et al,[56] 2001	Absence of severe daytime sleepiness and AHI 10-30/h	Parallel	No placebo	142	26	54	86	29	20	13	Office	129	82
Muxfeldt et al,[57] 2015	Resistant hypertension and AHI ≥15/h	Parallel	No placebo	125	26	61	40	33	41	11	Daytime	131	77
Nguyen et al,[58] 2010	ESS score >10 and RDI ≥15	Parallel	Sham CPAP	20	13	53	90	30	35	NA	Office	124	77
Noda et al,[59] 2007	Not taking antihypertensive medication and AHI ≥20/h	Parallel	No placebo	40	13	53	100	NA	47	NA	Office	144	89
Norman et al,[60] 2006	AHI >15/h	Parallel	Sham CPAP	33	2	50	85	31	61	12	Daytime	129	78
Pamidi et al,[61] 2015	Prediabetes and AHI ≥5/h	Parallel	Oral placebo	39	2	54	67	36	36	10	Daytime	140	83
Pedrosa et al,[62] 2013	Resistant hypertension and AHI ≥15/h	Parallel	No placebo	40	26	56	77	32	29	10	Daytime	147	87
Pepperell et al,[63] 2002	Male sex, ESS score >9, and ODI >10 dips/h	Parallel	Sham CPAP	118	4	51	100	35	37[d]	16	24 h	134	85
Robinson et al,[64] 2006	Hypertension, ESS score ≤10, and ODI >10 dips/h	Crossover	Sham CPAP	35	4	54	89	33	28[d]	5	24 h	142	86
Rossi et al,[65] 2013	CPAP use >4 h/night during past year and ODI >10 dips/h	Parallel	Provent placebo	45	2	62	78	34	39	14	Morning	131	83
Ruttanaumpawan et al,[66] 2008	Heart failure, AHI ≥20/h, and LVEF ≤45%	Parallel	No placebo	33	4	60	91	31	43	NA	Morning	126	66
Takaesu et al,[67] 2012	Panic disorder and AHI >20/h	Crossover	Sham CPAP	12	4	41	92	26	41	NA	Office	142	85
Weaver et al,[68] 2012	AHI 5-30/h and ESS score >10	Parallel	Sham CPAP	281	8	51	59	34	13	15	Daytime	124	76

Abbreviations: AHI, apnea hypopnea index; BP, blood pressure; LVEF, left ventricular ejection fraction; NA, not available or applicable; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

[a] Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.

[b] The Epworth Sleepiness Scale (ESS) has a score range of 0 to 24 (higher scores indicate greater daytime sleep propensity).

[c] Mean RDI was used because mean AHI and ODI were unavailable.

[d] Mean ODI was used because mean AHI was unavailable.

studies, 44 compared CPAP with an inactive control (4289 patients),[25-68] 3 compared MADs with an inactive control (229 patients),[69-71] 1 compared CPAP with MADs (126 patients),[72] and 3 compared CPAP, MADs, and an inactive control (244 patients)[11,12,73] (eFigure 1 in Supplement 2). All included studies assessed SBP as an outcome. One study[43] did not report DBP data. Summaries of the characteristics of the included trials appear in **Table 1** and **Table 2**. There was some evidence of a difference in the mean body mass index between trials of different treatment comparisons (**Table 3**); however, the differences between the weighted means were small. In particular, mean baseline BP was similar across comparisons. Thus, the consistency assumption in the network meta-analysis was not majorly violated in this regard.

Primary Analyses

The mean between-visit correlation across the 16 trials for which it could be estimated was 0.69 (minimum, 0.47 and maximum, 0.89) for SBP and 0.74 (minimum, 0.53 and maximum, 0.85) for DBP with the mean values being used to impute treatment effect standard errors in 25 studies. No inconsistency was found in the network meta-analysis of SBP (χ^2_3 = 0.54, P = .91) or DBP (χ^2_3 = 2.25, P = .52) and so the main conclusions were drawn from the consistency model. Although these tests for inconsistency are likely to be underpowered due to the small number of studies for some treatment comparisons, the relatively small values of the χ^2 statistics indicate that this is unlikely to be an issue in this case.

In the network meta-analysis and compared with an inactive control, CPAP was associated with a reduction in SBP of 2.5 mm Hg (95% CI, 1.5 to 3.5 mm Hg; P < .001) and MADs were associated with a reduction in SBP of 2.1 mm Hg (95% CI, 0.8 to 3.4 mm Hg; P = .002) (**Table 4**). In the network meta-analysis and compared with an inactive control, CPAP was associated with a reduction in DBP of 2.0 mm Hg (95% CI, 1.3 to 2.7 mm Hg; P < .001) and MADs were associated with a reduction in DBP of 1.9 mm Hg (95% CI, 0.5 to 3.2 mm Hg; P = .008). There was no significant difference between CPAP and MADs in their association with change in SBP (−0.5 mm Hg [95% CI, −2.0 to 1.0 mm Hg]; P = .55) or in DBP (−0.2 mm Hg [95% CI, −1.6 to 1.3 mm Hg]; P = .82).

The findings of the pairwise meta-analyses (Table 4) were similar to those of the network meta-analysis except for the comparison of MADs with inactive controls for reductions in DBP for which a smaller difference of −1.1 mm Hg (95% CI, −2.4 to 0.2 mm Hg; P = .11) was estimated. The results of each pairwise and network meta-analysis for SBP appear in **Figure 2** and **Figure 3** and for DBP in **Figure 4** and **Figure 5**.

A sensitivity analysis using the minimum and maximum between-visit correlation estimates (instead of the mean estimate) to impute missing treatment effect standard errors did not greatly affect the results of the network meta-analysis (eTables 1 and 2 in Supplement 2). Another sensitivity analysis in which the level of heterogeneity was assumed to be the same across comparisons only led to a slightly smaller estimated difference between MADs and inactive controls (eTable 3 in Supplement 2). This was likely due to

Table 2. Baseline Characteristics of Included Trials of Mandibular Advancement Devices (MADs) vs Continuous Positive Airway Pressure (CPAP) vs Inactive Control

Source	Main Inclusion Criteria	Type of Design	Type of Control Therapy	Sample Size	Length of Follow-up, wk	Mean Age, y	Male Sex, %	Mean BMI[a]	Mean AHI, /h	ESS Score[b]	Time or Location of BP Measurement	Mean Baseline BP, mm Hg	
												Systolic	Diastolic
MADs vs Inactive Control													
Andrén et al,[69] 2013	Hypertension and AHI ≥10/h	Parallel	Placebo MAD	72	13	58	79	30	24	11	Daytime	145	89
Gotsopoulos et al,[70] 2004	Mandibular protrusion ≥3 mm, AHI ≥10/h, and OSA symptoms	Crossover	Placebo MAD	67	4	48	79	29	27	NA	Daytime	132	81
Quinnell et al,[71] 2014	AHI 5-30/h and ESS score ≥9	Crossover	Placebo MAD	90	6	51	80	31	14	12	Office	130	80
CPAP vs MADs													
Phillips et al,[72] 2013	AHI >10/h and OSA symptoms	Crossover	NA	126	4	50	81	30	26	9	Morning	129	82
CPAP vs MADs vs Inactive Control													
Barnes et al,[11] 2004	AHI 5-30	Crossover	Oral placebo	104	13	46	79	31	22	11	24 h	127	76
Dal-Fabbro et al,[73] 2014	Mandibular protrusion ≥7 mm, AHI ≥20/h, and BMI ≤35	Crossover	Placebo MAD	39	4	47	83	28	42	NA	Daytime	133	83
Lam et al,[12] 2007	AHI 5-40/h and ESS score >9 if AHI 5-20/h	Parallel	No placebo	101	10	46	78	27	21	12	Morning	128	77

Abbreviations: AHI, apnea hypopnea index; BP, blood pressure; NA, not available or applicable; OSA, obstructive sleep apnea.

[a] Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.

[b] The Epworth Sleepiness Scale (ESS) has a score range of 0 to 24 (higher scores indicate greater daytime sleep propensity).

Table 3. Baseline Characteristics of Patients in Trials of Different Treatment Comparisons

	Weighted Mean (SD)				
	CPAP vs Inactive Control (n = 44 Trials)	MAD vs Inactive Control (n = 3 Trials)	CPAP vs MAD (n = 1 Trial)[a]	CPAP vs MAD vs Inactive Control (n = 3 Trials)	*P* Value
Length of follow-up, wk	15.1 (9.0)[b]	7.6 (4.6)	4.3	10.4 (3.7)	.30
Age, y	55.3 (6.3)	52.3 (5.0)	49.5	46.2 (0.6)	.14
Proportion of males	0.80 (0.13)	0.80 (0.01)	0.81	0.79 (0.02)	>.99
Body mass index[c]	32.1 (2.0)	29.8 (0.8)	29.5	29.1 (2.1)	.06
Apnea-hypopnea index, /h	36.9 (12.7)	20.7 (7.0)	25.6	24.8 (9.4)	.08
Oxygen desaturation index, dips/h	21.5 (9.9)	9.8[a]	20.8	12.8[a]	.68
Epworth Sleepiness Scale score[d]	10.1 (3.0)	11.5 (0.6)	9.1	11.1 (1.0)	.87
Blood pressure, mm Hg					
Systolic	132.6 (6.6)	135.0 (7.9)	129.2	127.9 (2.5)	.62
Diastolic	80.6 (4.1)	83.3 (4.8)	81.6	77.5 (2.9)	.48

Abbreviations: CPAP, continuous positive airway pressure; MAD, mandibular advancement device.

[a] Standard deviation is not reported if data from only 1 study was available.

[b] Two studies[46,55] with length of follow-up of 1 year or longer were excluded as outliers.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Score range of 0 to 24 (higher scores indicate greater daytime sleep propensity).

Table 4. Pairwise and Network Meta-analyses Comparing Treatment Effects on Changes in Systolic and Diastolic Blood Pressure

	No. of Trials	Sample Size	Type of Meta-analysis	Blood Pressure Difference (SE) [95% CI], mm Hg	*P* Value	Cochran χ^2 *P* Value[a]	I^2, %[a]	Between-Study Variance, τ^2
Systolic Blood Pressure								
CPAP vs inactive control	47	4533	Pairwise	−2.6 (0.5) [−3.6 to −1.6]	<.001	<.001	54	5.2
			Network	−2.5 (0.5) [−3.5 to −1.5]	<.001			5.0
MAD vs inactive control	6	473	Pairwise	−1.9 (0.7) [−3.2 to −0.6]	.004	.57	0	0
			Network	−2.1 (0.7) [−3.4 to −0.8]	.002			0.7
CPAP vs MAD	4	370	Pairwise	0.3 (0.6) [−1.0 to 1.5]	.68	.37	5	0.1
			Network	−0.5 (0.8) [−2.0 to 1.0]	.55			1.9
Diastolic Blood Pressure								
CPAP vs inactive control	46	4488	Pairwise	−2.1 (0.3) [−2.8 to −1.4]	<.001	<.001	52	2.1
			Network	−2.0 (0.4) [−2.7 to −1.3]	<.001			2.3
MAD vs inactive control	6	473	Pairwise	−1.1 (0.7) [−2.4 to 0.2]	.11	.11	45	1.2
			Network	−1.9 (0.7) [−3.2 to −0.5]	.008			1.3
CPAP vs MAD	4	370	Pairwise	0.2 (0.4) [−0.6 to 0.9]	.68	.46	0	0
			Network	−0.2 (0.7) [−1.6 to 1.3]	.82			0.1

Abbreviations: CPAP, continuous positive airway pressure; MAD, mandibular advancement device.

[a] Data correspond to pairwise meta-analysis only.

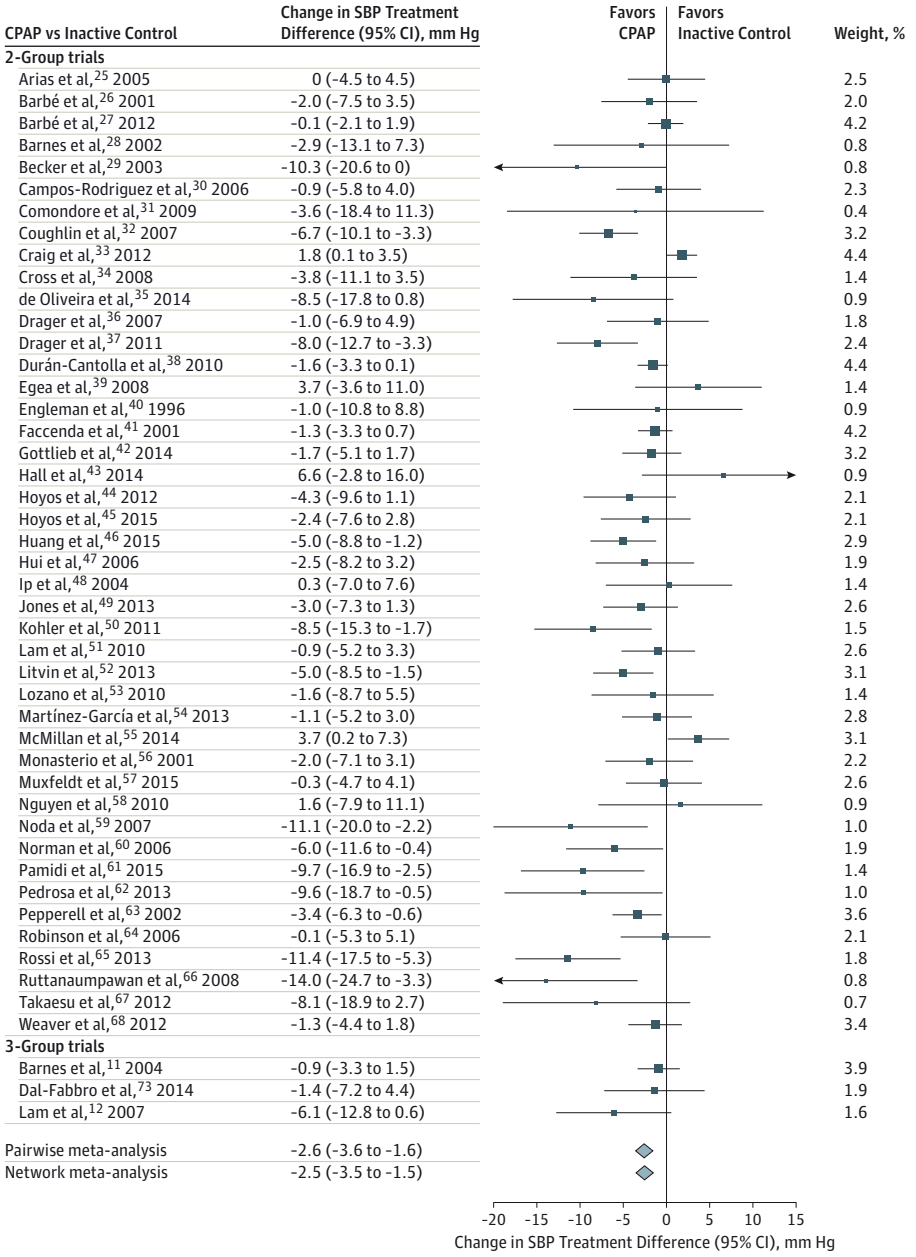
the increased weight of the smaller studies directly comparing these interventions, which tended to show treatment effects closer to the null than larger studies.

By applying a bootstrap procedure with 5000 draws to the main network analysis model, the probability of CPAP having the strongest association with SBP reduction was estimated to be 72%, whereas it was 28% for MADs. The probability of CPAP having the strongest association with DBP reduction was 58%, whereas it was 42% for MADs. Comparison-adjusted funnel plots for the network meta-analysis appear in eFigure 2 in Supplement 2. There is a small amount of asymmetry in the plot for DBP.

Meta-regression Analyses

Mean CPAP use (hours/night) could be obtained from 44 of the 47 studies comparing CPAP with an inactive control. The associations between the mean CPAP use and the treatment effects on BP reported in these studies appear in **Figure 6**. A 1-hour-per-night increase in mean CPAP use was associated with an additional reduction in SBP of 1.5 mm Hg (95% CI, 0.8 to 2.3 mm Hg; $P < .001$) and an additional reduction in DBP of 0.9 mm Hg (95% CI, 0.3 to 1.4 mm Hg; $P = .001$). There was evidence of an association between length of follow-up and the reported effects of CPAP on SBP (slope, 0.2 mm Hg per 1-week increase [95% CI, 0.1 to 0.3 mm Hg];

Figure 2. Treatment Effect for Change in Systolic Blood Pressure (SBP) in the Included Trials of Continuous Positive Airway Pressure (CPAP) vs Inactive Control



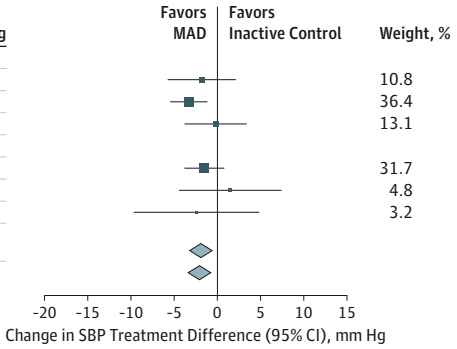
The size of each data marker is proportional to the weight carried by the corresponding study in the random-effects pairwise meta-analysis.

P = .003) and on DBP (slope, 0.1 mm Hg [95% CI, 0 to 0.2 mm Hg]; P = .006) with the reported treatment effects trending toward zero as length of follow-up increased (eFigure 3 in Supplement 2). Studies with smaller sample sizes tended to report higher mean compliance (correlation with sample size, r = −0.30) and had shorter follow-up periods (r = 0.19). Thus, the reported treatment effect of CPAP was likely to be larger in smaller studies, which may be the reason for the asymmetry in the funnel plots in eFigure 2 rather than publication bias.

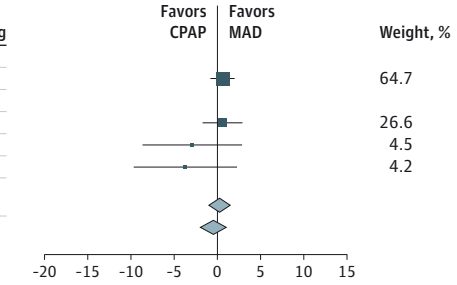
There were statistically significant associations between the reported effect of CPAP on SBP and mean baseline SBP (slope, −0.2 mm Hg [95% CI, −0.3 to 0 mm Hg]; P = .04) and between the reported treatment effect on DBP and mean baseline DBP (slope, −0.2 mm Hg [95% CI, −0.4 to 0 mm Hg]; P = .01) (eFigure 4 in Supplement 2). A total of 11 of the 47 studies (23%) comparing CPAP with an inactive control included only patients with some form of hypertension. In a post hoc analysis, we found no difference between the reported treatment effects in this subgroup of trials compared with those with no such inclusion requirement on SBP (−0.8 mm Hg [95% CI, −3.1 to 1.5 mm Hg]; P = .50) or on DBP (−0.6 mm Hg [95% CI, −2.2 to 1.0 mm Hg]; P = .47). There was no association of either the mean baseline

Figure 3. Treatment Effect for Change in Systolic Blood Pressure (SBP) in the Included Trials of Mandibular Advancement Device (MAD) vs Continuous Positive Airway Pressure (CPAP) and vs Inactive Controls

MAD vs Inactive Control	Change in SBP Treatment Difference (95% CI), mm Hg
2-Group trials	
Andrén et al,[69] 2013	-1.8 (-5.8 to 2.2)
Gotsopoulos et al,[70] 2004	-3.3 (-5.5 to -1.1)
Quinnell et al,[71] 2014	-0.2 (-3.8 to 3.4)
3-Group trials	
Barnes et al,[11] 2004	-1.5 (-3.8 to 0.8)
Dal-Fabbro et al,[73] 2014	1.5 (-4.4 to 7.4)
Lam et al,[12] 2007	-2.4 (-9.7 to 4.9)
Pairwise meta-analysis	-1.9 (-3.2 to -0.6)
Network meta-analysis	-2.1 (-3.4 to -0.8)



CPAP vs MAD	Change in SBP Treatment Difference (95% CI), mm Hg
2-Group trial	
Phillips et al,[72] 2013	0.6 (-0.8 to 2.0)
3-Group trials	
Barnes et al,[11] 2004	0.6 (-1.7 to 2.9)
Dal-Fabbro et al,[73] 2014	-2.9 (-8.7 to 2.9)
Lam et al,[12] 2007	-3.7 (-9.7 to 2.3)
Pairwise meta-analysis	0.3 (-1.0 to 1.5)
Network meta-analysis	-0.5 (-2.0 to 1.0)



The size of each data marker is proportional to the weight carried by the corresponding study in the random-effects pairwise meta-analysis.

apnea-hypopnea index or the oxygen desaturation index in each study with the reported treatment effects of CPAP on SBP and DBP (eFigures 5 and 6 in Supplement 2). Thus, despite there being some evidence of the mean apnea-hypopnea index differing between treatment comparisons (Table 3), this lack of association implies that the consistency assumption of the network meta-analysis was not likely to be violated.

Of the 47 trials comparing CPAP with an inactive control, 22 used sham CPAP as the comparator. The remaining 25 studies used either no treatment (n = 18), an oral placebo (n = 5), a placebo oral appliance (n = 1), or an expiratory nasal resistance valve placebo (n = 1). There were no statistically significant differences in the reported effects of CPAP on SBP or DBP between trials using sham CPAP, any other type of placebo or no placebo as the comparator (eTable 4 in Supplement 2).

Data on daytime ambulatory BP measurements could be extracted from 20 of the 47 studies comparing CPAP with an inactive control, and only 24-hour data could be obtained in 6 studies. A post hoc analysis showed that the association of CPAP with reduction in BP in these 6 studies did not differ compared with those in which daytime BP data was obtained; however, there was some suggestion that the effect of CPAP reported in the studies was larger in those in which morning BP data was extracted (eTable 5 in Supplement 2). Applying the adjustment method by Knapp and Hartung[20] in a sensitivity analysis made little difference in the findings of the meta-regression analyses, increasing the standard error of the meta-regression coefficients by no more than 9% in the analyses for SBP and by no more than 12% for DBP.

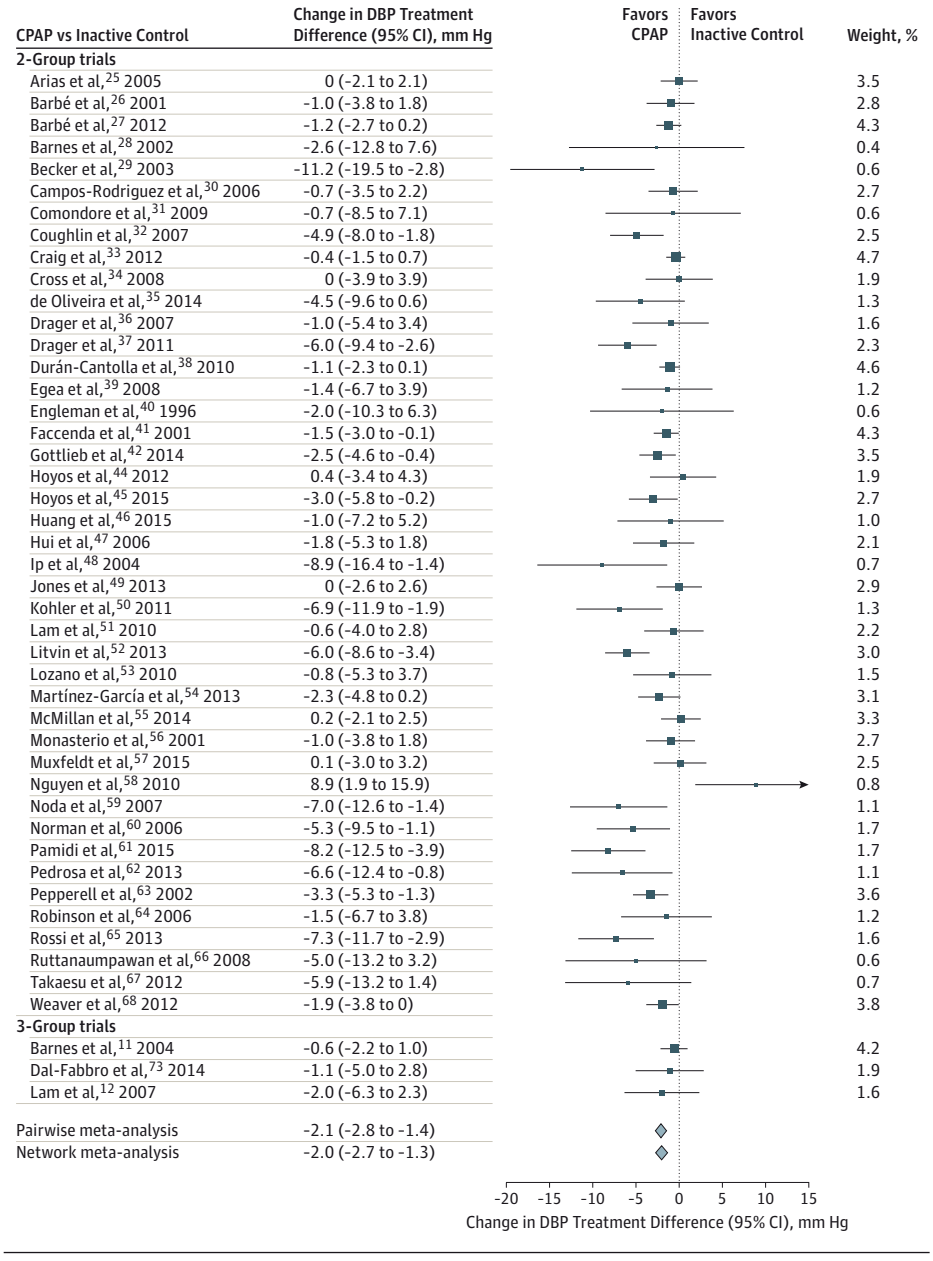
Risk of Bias Assessment

No more than 5 of the included trials (<10%) were deemed to be at high risk of bias in only 3 domains (allocation concealment, incomplete outcome data, selective reporting) of the Cochrane Collaboration risk of bias tool (eTable 6 and eFigure 7 in Supplement 2). In most domains, the majority of trials were at low risk, except for the allocation concealment category in which most trials were at an unclear risk due to inadequate reporting of methods. Due to either the small number or the absence of any high-risk studies in each domain, reported treatment effects were not compared between trials at high and low risk of bias.

Discussion

To our knowledge, this is the first network meta-analysis comparing CPAP, MADs, and inactive controls on BP in patients with obstructive sleep apnea. We found that both CPAP and MADs were associated with similar reductions in SBP and DBP compared with an inactive treatment. This is partly in contrast to a previous meta-analysis,[10] which did not find a beneficial association with MADs, perhaps due to including only 2 RCTs and thus having inadequate power to detect a difference. Even though there was no statistically

Figure 4. Treatment Effect for Change in Diastolic Blood Pressure (DBP) in the Included Trials of Continuous Positive Airway Pressure (CPAP) vs Inactive Control



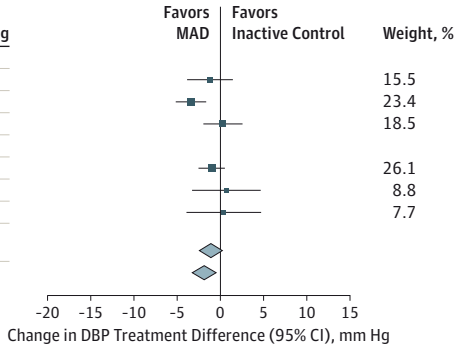
The size of each data marker is proportional to the weight carried by the corresponding study in the random-effects pairwise meta-analysis.

significant difference between the associations of CPAP and MADs with change in BP in our meta-analysis, CPAP had a considerably higher probability of having the strongest association with SBP reduction. The associations of both CPAP and MADs with DBP reduction were more similar; however, the association of CPAP with reductions of both SBP and DBP is likely to be greater in patients using CPAP for longer periods at night or in those with higher baseline BP levels.

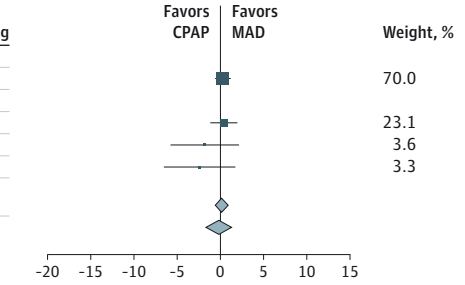
Even though the results of the pairwise and network meta-analyses were mostly similar, the biggest difference was seen in the comparison of MADs with inactive controls on DBP with the network model estimating a larger association than the pairwise meta-analysis. This was most likely because the data from the direct comparisons of CPAP and MADs tended to favor MADs, and so incorporating these data in the network meta-analysis increased the difference between MADs and inactive controls on change in DBP. In addition, because the difference between CPAP and inactive controls in the pairwise analyses was substantially larger than that for MADs, the comparison between CPAP and MADs changed to favor CPAP in the network meta-analysis (albeit not to a statistically significant extent). The precision of the comparison between CPAP and MAD was slightly lower in the network meta-analyses than when considering direct evidence alone, which may be due to the large amount of

Figure 5. Treatment Effect for Change in Diastolic Blood Pressure (DBP) in the Included Trials of Mandibular Advancement Device (MAD) vs Continuous Positive Airway Pressure (CPAP) and vs Inactive Controls

MAD vs Inactive Control	Change in DBP Treatment Difference (95% CI), mm Hg	Weight, %
2-Group trials		
Andrén et al,[69] 2013	-1.2 (-3.9 to 1.5)	15.5
Gotsopoulos et al,[70] 2004	-3.4 (-5.2 to -1.6)	23.4
Quinnell et al,[71] 2014	0.3 (-2.0 to 2.6)	18.5
3-Group trials		
Barnes et al,[11] 2004	-1.0 (-2.5 to 0.5)	26.1
Dal-Fabbro et al,[73] 2014	0.7 (-3.3 to 4.7)	8.8
Lam et al,[12] 2007	0.4 (-3.9 to 4.7)	7.7
Pairwise meta-analysis	-1.1 (-2.4 to 0.2)	
Network meta-analysis	-1.9 (-3.2 to -0.5)	

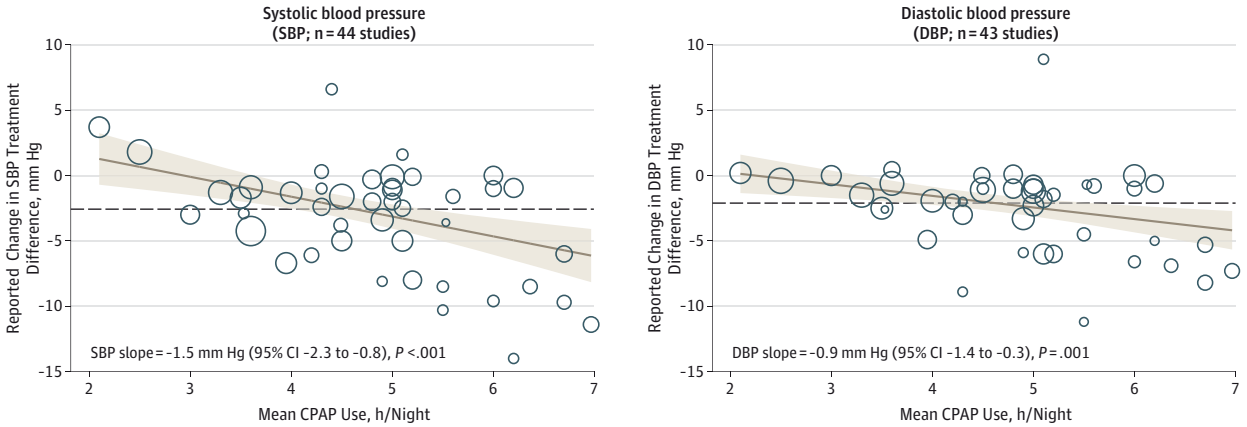


CPAP vs MAD	Change in DBP Treatment Difference (95% CI), mm Hg	Weight, %
2-Group trial		
Phillips et al,[72] 2013	0.3 (-0.6 to 1.2)	70.0
3-Group trials		
Barnes et al,[11] 2004	0.4 (-1.2 to 2.0)	23.1
Dal-Fabbro et al,[73] 2014	-1.8 (-5.8 to 2.2)	3.6
Lam et al,[12] 2007	-2.4 (-6.5 to 1.7)	3.3
Pairwise meta-analysis	0.2 (-0.6 to 0.9)	
Network meta-analysis	-0.2 (-1.6 to 1.3)	



The size of each data marker is proportional to the weight carried by the corresponding study in the random-effects pairwise meta-analysis.

Figure 6. Association Between Use of Continuous Positive Airway Pressure (CPAP) on Change in Systolic Blood Pressure and Diastolic Blood Pressure



Circles represent individual results for each trial with the size of the circle being proportional to its weight in the random-effects meta-analysis. Each meta-regression line (solid lines) and its 95% confidence interval (shaded areas) were estimated using a random-effects linear meta-regression model with mean use of CPAP as the covariate. The dashed lines represent the overall difference. Treatment difference data are CPAP minus inactive control.

between-study variation observed in the indirect comparisons being incorporated into the analysis.

Our meta-regression analyses showed that studies in patients with higher mean use of CPAP or higher baseline BP level tended to report more beneficial treatment effects of CPAP on SBP and DBP. However, it should be noted that meta-regression analyses of mean patient characteristics do not necessarily demonstrate the dose-response relationship at a patient level and so it is possible that the same associations found herein would not have been observed in many of the individual trials.[74] For instance, in contrast to our findings, a previous meta-analysis[75] investigating the effect of CPAP in asymptomatic patients using individual patient data did not detect a difference between outcomes in patients using CPAP more or less than 4 hours/night compared with controls. Repeating our network meta-analysis

using individual patient data rather than aggregate data would improve the assessment of the association of CPAP use and other patient characteristics with each treatment comparison but would be challenging to conduct due to the large number of RCTs from which to acquire data. Alternatively, conducting an RCT in which patients are given various durations of CPAP therapy each night will provide an unbiased assessment of whether there is a dose-response relationship with BP but also might prove challenging to conduct.

Compared with the most recent meta-analysis[5] on this topic with similar inclusion criteria, our study includes 18 more RCTs of CPAP and includes at least an additional 2700 patients. Therefore, we had considerably more power to assess the association of trial-level characteristics, such as mean CPAP use, with the reported treatment effects on SBP and DBP. We have also used data from 6 trials comparing MADs with an inactive control, which is considerably more than the 2 trials used in a previous meta-analysis.[10] Although only 4 RCTs directly compared CPAP with MADs, we have attempted to strengthen this and all other comparisons by incorporating indirect evidence using a network meta-analysis. Furthermore, in contrast to separate pairwise analyses, we have been able to rank each treatment based on the strength of its association with reductions in SBP and DBP.

A limitation of our meta-analysis is that we only investigated 2 active treatments (ie, CPAP and MADs) and excluded other treatments, such as weight loss interventions,[76] which are likely to have beneficial effects on BP because they have been shown to have favorable effects on decreasing the severity of obstructive sleep apnea. However, few trials of other interventions exist and so including them would have increased the sparseness of the network meta-analysis, which can lead to modeling problems, particularly with regard to estimating the between-trial variance of treatments that were not directly compared. Another limitation was that we were unable to extract daytime ambulatory BP data from all studies and thus had to use the available morning, office, or 24-hour measurements. Although this may have increased heterogeneity, it allowed all of the relatively few studies investigating MADs to be incorporated into the analyses. A subgroup analysis showed some evidence that studies from which we extracted morning BP reported slightly larger treatment effects than in other studies. However, there was no difference with studies in which we extracted 24-hour ambulatory measurements and so the effect of any nighttime BP variability was negligible. Future meta-analyses could analyze each BP measurement separately to better understand whether each treatment is associated with greater reductions in BP during the daytime or nighttime.

Our results were robust to the assumed between-visit correlation, which was estimated from parallel trials. However, for simplicity, we did not estimate the between-period correlation from crossover trials (reporting treatment effects from paired *t* tests) and then use that estimate when calculating treatment effects in other crossover studies. Although this could be deemed a limitation of our analyses, assuming a between-period correlation of zero is arguably reasonable when considering changes from baseline.[77] In addition, because only a small proportion of crossover studies were treated this way, we do not believe that our results are sensitive to this assumption.

Conclusions

Among patients with obstructive sleep apnea, both CPAP and MADs were associated with reductions in BP. Network meta-analysis did not identify a statistically significant difference between the BP outcomes associated with these therapies.

ARTICLE INFORMATION

Author Contributions: Dr Bratton had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bratton, Kohler.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bratton.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bratton.
Obtained funding: Kohler.
Administrative, technical, or material support: Gaisl, Kohler.
Study supervision: Kohler.

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