

TITLE: Continuous Positive Airway Pressure Compared with Oral Devices or Lifestyle Changes for the Treatment of Obstructive Sleep Apnea: A Review of the Clinical and Cost-effectiveness

DATE: 22 December 2014

CONTEXT AND POLICY ISSUES

Obstructive sleep apnea (OSA) is a condition in which the repetitive, partial, or complete closure of the upper airway results in repeated, reversible blood oxygen desaturation and sleep fragmentation.¹ The prevalence of OSA, defined by an apnea-hypopnea index (AHI) ≥ 5 events/hour, was 9% in women and 24% in men in a random sample of Wisconsin state employees ages 30 to 60 years, and is increased with male gender, obesity, and age.² When defined as a clinical syndrome (AHI ≥ 5 events/hour combined with significant sleepiness), OSA has a prevalence of 2% in women and 4% in men.² A Canadian Community Health Survey in 2009 reported a 3% prevalence of OSA in Canadians adults.³ OSA is determined by a number of sleep parameter abnormalities measured by polysomnography such as AHI, arousal index, and minimum oxygen saturation (S_{PO_2}).² OSA is associated with neurobehavioral morbidities reflected by a reduction in the Epworth Sleepiness Score (ESS) and quality of life; increased cardiovascular diseases such as high blood pressure, heart failure; and metabolic morbidities such as oxidative stress.⁴ OSA is associated with substantial costs to society due to its morbidities, with costs of untreated OSA potentially doubling medical expenses, mainly because of cardiovascular diseases.⁵ OSA-related motor vehicle collisions in 2000 were estimated at US\$15.9 billion in damages and health-related costs.²

Treatment of OSA includes a wide range of options, such as changes in diet and lifestyle to reduce risk factors for OSA, pharmacotherapy, the use of continuous airway pressure (CPAP) and various oral devices to splint the airway open to facilitate airflow, to upper airway surgical treatment.^{6,7} In Ontario, patients waited a mean 11.6 months from the time being referred to a sleep clinic to the time of medical therapy initiation, and 16.2 months to surgical therapy initiation.⁸

This Rapid Response report aims to review the clinical and cost-effectiveness of CPAP as compared to oral devices and lifestyle changes in the treatment of OSA.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness of continuous positive airway pressure (CPAP) compared with oral devices for the treatment of sleep apnea?
2. What is the clinical effectiveness of CPAP compared with lifestyle changes for the treatment of sleep apnea?
3. What is the cost-effectiveness of CPAP compared with oral devices or lifestyle changes for the treatment of sleep apnea?

KEY FINDINGS

In general, results from the controlled setting of RCTs and systematic reviews of RCTs found that CPAP lead to better efficacy than oral devices. This benefit may be offset by patient's higher compliance to oral devices which may result in similar real-life clinical effectiveness. CPAP may be more costly than oral devices or lifestyle advice, and oral devices may be a more cost-effective option in patients who are unable to adhere to CPAP. The small number of trials included in the report, the significant heterogeneity between the included trials for many outcomes, the difference in length of follow-up periods, and the potential difference in costs, treatment effect and adherence of various types of oral appliances caution the interpretation of the results.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and November 21, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles or abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients with moderate to severe sleep apnea
Intervention	CPAP
Comparator	Oral devices Lifestyle changes (e.g. diet and exercise)
Outcomes	Clinical effectiveness (e.g. measured by ESS, arousal index, or changes in blood pressure), safety, cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and economic evaluations were selected for inclusion.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2009, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews, RCTs and cost-effectiveness studies was assessed using the AMSTAR,⁹ Downs and Black,¹⁰ and Drummond¹¹ checklists, respectively. Numerical scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 542 citations. After screening of abstracts from the literature search and from other sources, 16 potentially relevant studies were selected for full-text review. Seven studies met the inclusion criteria and were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 2.

Study design

The literature search identified two systematic reviews/meta-analysis,^{12,13} three RCTs,¹⁴⁻¹⁶ and two cost-effectiveness studies.^{17,18} The systematic reviews performed literature searches up to September,¹² and October 2012¹³ and included 14 and three RCTs, respectively. The RCTs were published in 2013 and 2014, and were not reported in the systematic reviews.



Population

All studies included adult patients with moderate to severe OSA.¹²⁻¹⁸ Baseline AHI inclusion criteria varied across studies, ranging from 5 to 30 events per hour.

Interventions and comparators

Interventions and comparators were CPAP,¹²⁻¹⁸ oral devices¹²⁻¹⁸ and lifestyle interventions (dietary habits and lifestyle such as posture and exercise).¹⁸

Outcomes

The systematic reviews and RCTs reported polysomnographic (including AHI, arousal index, minimum S_{pO_2} , rapid eye movement sleep rate),^{12,14-16} neurobehavioral (including ESS score, health-related quality of life [QoL]),¹²⁻¹⁶ cardiovascular (blood pressure),^{12,14,15} compliance rate,¹⁴ treatment usage, preference, side effects, withdrawals,¹² weight reduction,¹³ and BMI.¹³ The cost studies reported costs, quality-adjusted life years (QALY), incremental cost-effectiveness ratios (ICER), and sensitivity analysis outcomes.^{17,18} In one cost study, only direct medical costs were considered, with a time horizon of five years.¹⁷ In the second cost study, costs comprised the costs of the interventions and the healthcare resources used for strokes, coronary heart diseases, and road traffic accidents, with a patient lifetime horizon.¹⁸

Summary of Critical Appraisal

In general, the meta-analyses including in this report is rigorous with limited potential bias due to the inclusion of randomized controlled trials and the independent data extraction process.^{12,13} The systematic reviews each had a comprehensive literature search and explicit inclusion and exclusion criteria. Both meta-analyses included a small number of studies which may limit the robustness of the findings. Neither meta-analysis analyses took into account difference in oral appliances designs among the included trials, or reported on the likelihood of publication bias. Comparative analyses were not adjusted for the baseline differences in patient characteristics. The included randomized controlled trials were small in size, and short period of follow-up, except one with 2 year follow-up.¹⁶ Assessors was blinded to the intervention in one single-blinded RCT,¹⁴ while the other two RCTs were open-label in design.^{15,16} The economic evaluation studies in general provided a good appraisal of the cost-effectiveness of CPAP compared to oral devices and lifestyle changes.^{17,18} The cost estimates was based on survey data from 1997, and may not be reflective of current costs. Potential differences in costs, treatment effect and adherence of various types of oral devices were not considered, limiting the generalizability of the findings.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the clinical effectiveness of CPAP compared with oral devices for the treatment of sleep apnea?



One systematic review/meta-analysis¹² and three RCTs¹⁴⁻¹⁶ compared the clinical effectiveness of CPAP to oral devices in the treatment of moderate to severe OSA. In general, results from controlled setting of RCTs found that CPAP had better efficacy than oral devices defined as a significant reduction in AHI. This benefit may be offset by patient's higher compliance to oral devices which may result in similar real life clinical effectiveness.

The systematic review, with literature search up to September 2012, included 14 RCTs that compared clinical outcomes of CPAP and oral devices comprising mainly of mandibular advancement device (MAD) in patients with moderate to severe OSA.¹² Pooled estimates from meta-analysis showed that CPAP lead to statistically significant better AHI compared to oral devices but other polysomnographic outcomes such as arousal index, minimum S_{pO₂}, or rapid eye movement sleep rate had inconsistent findings among trials. Neurobehavioral and cardiovascular outcomes such as ESS score, health-related QoL, cognitive performance, blood pressure were similar between oral appliances (OA) and CPAP (differences not statistically significant). The review did not find statistically significant differences in treatment usage, treatment preference, side effects, and withdrawals between OA and CPAP.

A 2014 randomized, single-blind, cross-over, controlled study on 29 adults with moderate to severe OSA compared polysomnographic, neurobehavioral, and cardiovascular outcomes, and compliance rate between CPAP and MAD.¹⁴ Data measured one month after the end of each treatment phase showed statistically significant difference between CPAP and OA in polysomnographic outcomes (AHI, stage 2 sleep %, arousal index, apnea-hypopnea events and minimum S_{pO₂}, in favour of CPAP. There were no statistically significant differences in neurobehavioral and cardiovascular outcomes between the two methods. No statistically significant difference between CPAP and MAD in oxidative stress parameters such as lipid peroxidation products, erythrocyte superoxide dismutase activity. MAD led to better compliance than CPAP (differences statistically significant).

A 2013 randomized, open-label, cross-over, controlled study on 108 adults with moderate to severe OSA compared polysomnographic, neurobehavioral, and cardiovascular outcomes, and compliance rate between CPAP and MAD.¹⁵ Data measured after one month at the end of each treatment phase showed a statistically significant difference between CPAP and MAD in polysomnography outcomes (AHI, arousal index, total sleep time, and minimum S_{pO₂}), in favour of CPAP. There was no statistically significant difference between the two methods in cardiovascular outcomes and ESS. MAD led to a statistically significant improvement in four general quality-of-life domains and compliance rate compared to CPAP.

A 2013 randomized, open-label, controlled study on 103 adults with mild to severe OSA compared polysomnographic and neurobehavioral outcomes between CPAP and MAD.¹⁶ Data measured after one and two years of treatment showed that, except minimum S_{pO₂} that favored CPAP, data showed similar polysomnographic and neurobehavioral outcomes (ESS, QoL) between CPAP and MAD after 2 years follow-up (differences not statistically significant).

2. What is the clinical effectiveness of CPAP compared with lifestyle changes for the treatment of sleep apnea?

A systematic review with literature search up to October 2012 included three RCTs that compared clinical outcomes of CPAP + diet to diet alone in patients with moderate to severe OSA.¹³ Pooled estimates from meta-analysis showed that CPAP plus diet reduced weight and BMI compared to diet alone (the differences were statistically significant). Neurobehavioral

outcomes (ESS, QoL) were similar between the two arms (differences not statistically significant)

3. What is the cost-effectiveness of CPAP compared with oral devices or lifestyle changes for the treatment of sleep apnea?

Two 2009 economic studies calculated costs and cost-effectiveness of CPAP compared to oral devices,¹⁷ and CPAP compared to oral devices or lifestyle advice¹⁸ in the treatment of adult patients with moderate to severe OSA. In general, the studies suggest that CPAP is more costly than oral devices or lifestyle advice, and oral devices may be a more cost-effective option in patients who are unable to adhere to CPAP.

In the study conducted in Canada and the UK,¹⁷ CPAP resulted in \$1,917 more direct costs than OA, and increased 0.0696 QALY compared to OA (direct medical costs obtained from 2000 report of the National Traffic Safety Administration; estimates using 2004 US \$), based on data from RCTs with efficacy defined as the relative reduction of AHI. CPAP was more cost-effective compared to OA (ICER < \$50,000/QALY) in most scenarios, except when the gain in utility was assumed to be equal between CPAP and OA. If adherence to OA was at least 80% and adherence to CPAP was only 70%, OA became more cost-effective.

In the study conducted in the UK,¹⁸ CPAP resulted in an increase of £504 in medical direct costs compared to dental devices, and £1,161 compared to lifestyle advice (cost estimates using 2005-2006 £). CPAP increased 0.13 QALY compared to dental devices and increased 0.46 QALY compared to lifestyle advice, based on data from RCTs with efficacy defined as the relative reduction of AHI. CPAP was more cost effective compared to dental devices or lifestyle advice (ICER <£20,000/QALY) in all scenarios, except in the mild disease group.

Limitations

Data were on a population with moderate to severe OSA, and there were no specific data on moderate OSA population, therefore generalizability to particular classifications of OSA is unclear. The small number of trials included in the report, the significant heterogeneity between the included trials for many outcomes, and the difference in length of follow-up periods cautions the interpretation of the results. Difference in designs of oral devices was not taken into consideration in the analyses. The included systematic reviews did not perform funnel plot for pooled estimates to assess the potential publication bias may exaggerate the effectiveness of the intervention. The cost studies did not take into consideration potential differences in costs, treatment effect and adherence of various types of oral appliances.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In general, limited evidence from a small number of RCTs and systematic reviews of RCTs found that in a controlled setting, CPAP lead to better efficacy than oral devices. This benefit may be offset by patient's higher compliance to oral devices which may result in similar real life clinical effectiveness between the two methods. CPAP may be more costly than oral devices or lifestyle advice, and oral devices may be a more cost-effective option in patients who are unable to adhere to CPAP.

Matching therapy to patient's preferences is important to determine the most appropriate treatment, which in turn will increase the chance of adherence to the treatment. A qualitative



survey using focus group sessions found that patients with OSA expressed six expectations for treatment, listed in order of most to least frequently mentioned: improved health, apnea elimination, improved sleep, reduced fatigue, reduced snoring, and bed partner benefits.¹⁹ This study showed that patients may weight factors differently from practitioners in regards to the choice for OSA treatment options, and tailored intervention is needed for each individual.

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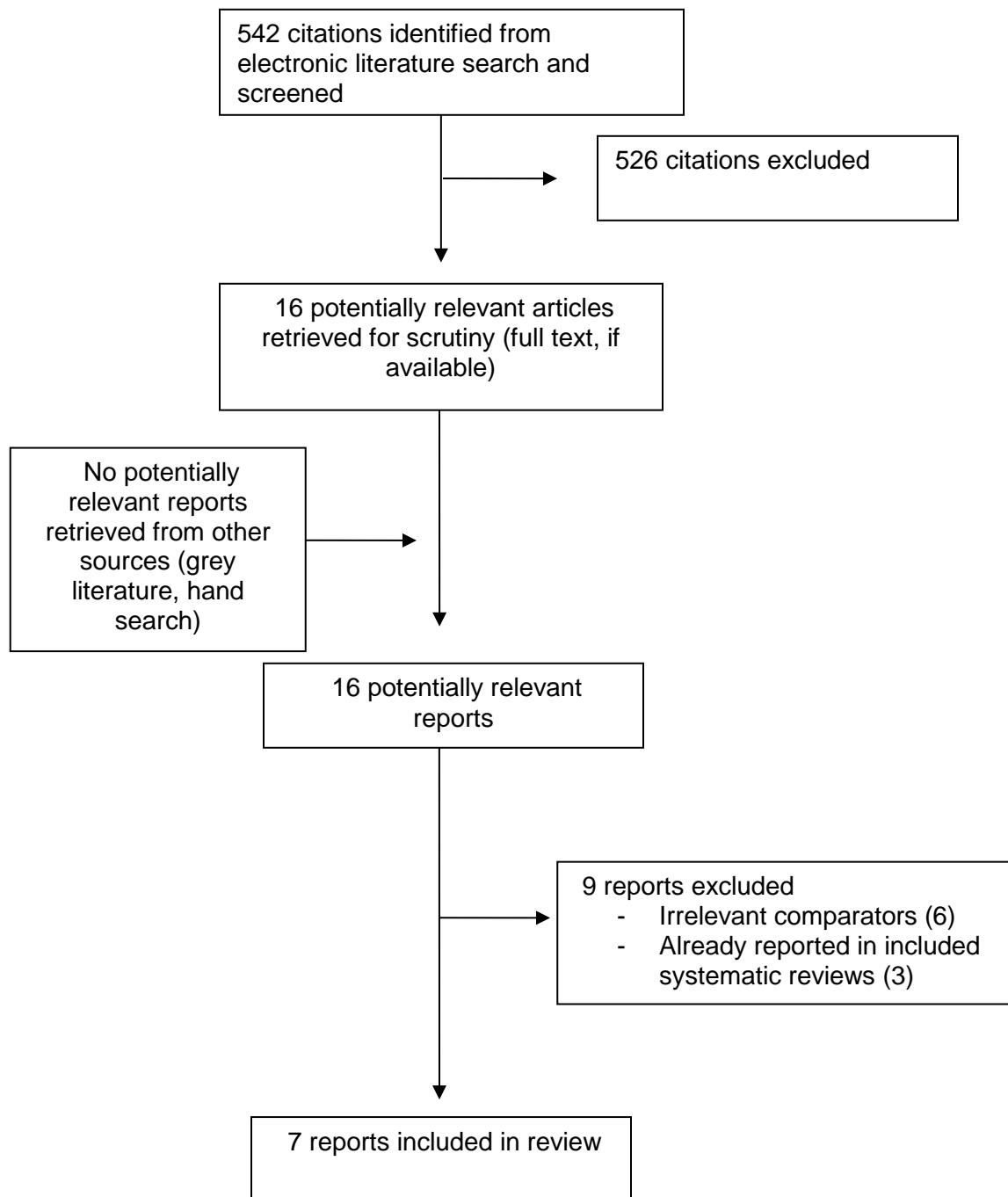


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Appendix 1: Selection of Included Studies

Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included Systematic Reviews

First Author, Year, Country,	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Studies included Main outcomes
Li, ¹² 2013, China	<i>"Relevant studies were retrieved from the following electronic databases, up to and including September 2012: MEDLINE, PubMed, EMBASE, and Central Register of Controlled Trials" (p 1184)</i>	<i>"The inclusion criteria were:</i> <ul style="list-style-type: none"> • 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" (p 1185) 	Studies not fulfilling the inclusion criteria	Fourteen studies comparing CPAP to oral appliances included in the review <i>"The main outcomes were Epworth Sleepiness Scale score, health-related quality of life, cognitive performance, blood pressure, apnea-hypopnea index (AHI), arousal index, minimum SpO₂, percent rapid eye movement sleep, treatment usage, side effects, treatment preference, and withdrawals" (p 1184)</i>
Thomasouli, ¹³ 2013, UK	<i>"Detailed individual search strategies for each of the following bibliographic databases were developed: OVIDSP Medline (1996 to October 2012), OVIDSP Embase (1996 to October 2012) the Cumulative Index to Nursing and Allied Health Literature-CINAHL (from inception to October 2012) and the Cochrane library Including CENTRAL, CDSR and DARE databases (from inception to October 2012)" (p 926)</i>	<i>"Randomised controlled trials with an intervention based on dietary weight loss, exercise and/or lifestyle programme of at least 2 months follow-up in adult subjects (≥ 18 years of age) with OSA and a disease severity index of an AHI≥ 5 were eligible for inclusion. A language restriction was applied, and only studies in the English language which met the inclusion criteria were considered in this review" (p 926)</i>	Studies not fulfilling the inclusion criteria	Three studies comparing CPAP + diet to diet alone included in the review Weight BMI QoL Epworth Sleepiness Scale

BMI = body mass index; QoL = quality of life

Table A2: Characteristics of Included RCTs

First Author, Year, Country,	Sample Size, Patient Characteristics, Length of Follow-up	Intervention	Comparator(s)	Main Study Outcomes
Dal-Fabbro, ¹⁴ 2014, Brazil	Randomized, cross-over, single-blind, controlled study 29 adults with moderate to severe OSA 1 month follow-up Outcomes measured at baseline and after treatment	CPAP	MAD	Polysomnographic outcomes (sleep parameters) Neurobehavioral outcomes (ESS) Cardiovascular outcomes (BP, HRV) Oxidative stress (lipid peroxidation products, erythrocyte catalase activity) Compliance for devices
Phillips, ¹⁵ 2013, Australia	Randomized, cross-over, open-label, controlled study 108 adults with moderate to severe OSA 1 month follow-up Outcomes measured at baseline and after treatment	CPAP	MAD	Polysomnographic outcomes (sleep parameters) Neurobehavioral outcomes (ESS, QoL) Cardiovascular outcomes (BP, arterial stiffness)
Doff, ¹⁶ 2013, The Netherlands	Randomized, open-label, controlled study 103 adults with mild to severe OSA 2 years follow-up Outcomes measured at baseline and after 1 and 2 years of treatment	CPAP	MAD	Polysomnographic outcomes (sleep parameters) Neurobehavioral outcomes (ESS, QoL)

BP = blood pressure; CPAP = continuous air way pressure; ESS = Epworth sleeping scale; HRV = heart rate variability; MAD = mandibular advancement device; OSA = obstructive sleep apnea; QoL = quality of life; RCTs = randomized controlled trials

Table A3: Characteristics of Included Cost-effectiveness Studies

First Author, Year, Country,	Study Objectives	Interventions/Comparators	Patients, perspective, time-horizon	Main Study Outcomes
Sadatsafavi, ¹⁷ 2009, Canada, UK	<i>"Oral appliances (OA) are commonly prescribed for the treatment of obstructive sleep apnoea-hypopnoea (OSAH), but there is limited evidence on their cost-effectiveness" (p 241)</i>	OAs (types not specified) CPAP	Adults with moderate to severe OSA Perspective of a third-party payer in the USA (only direct medical costs considered) 5-year time-horizon	Cost QALY ICER
Weatherly, ¹⁸ 2009, UK	<i>"This study reports on the cost-effectiveness of CPAP compared with dental devices and lifestyle advice" (p 26)</i>	CPAP Dental devices (types not specified) Lifestyle advice	Adults with moderate to severe OSA Perspective of NHS and Personal Society Services (interventions and costs for stroke, CHD, and RTA considered) Patient lifetime horizon	Cost QALY ICER

CHD: coronary heart disease; CPAP: continuous positive airway pressure; ICER: incremental cost-effectiveness ratio; NHS: UK National Health Services; OA: oral appliances; OSA: obstructive sleep apnea; QALY: quality-adjusted life year; RTA: road traffic accident

Appendix 3: Summary of Critical Appraisal of Included Study

Table A4: Summary of Critical Appraisal of Included Study

First Author, Publication Year	Strengths	Limitations
Systematic Reviews (AMSTAR)		
Li, ¹² 2013	<ul style="list-style-type: none"> • randomized controlled studies only were included • a priori design was provided • independent data extractors • comprehensive literature search • status of publication was used as an inclusion criterion • list of included studies provided • characteristics of included studies provided • quality of the included studies documented • methods to combine findings were appropriate • conflict of interest was stated 	<ul style="list-style-type: none"> • small sample size of the included trials and small number of trials • list of excluded studies not provided • analyses did not take into account difference in oral appliances designs among the included trials • likelihood of publication bias was not assessed
Thomasouli, ¹³ 2013	<ul style="list-style-type: none"> • randomized controlled studies only were included • a priori design was provided • independent data extractors • comprehensive literature search • status of publication was used as an inclusion criterion • list of included studies provided • characteristics of included studies provided • methods to combine findings were appropriate • conflict of interest was stated 	<ul style="list-style-type: none"> • small sample size of the included trials and small number of trials • list of excluded studies not provided • quality of the included studies not documented • analyses did not take into account difference in oral appliances designs among the included trials • likelihood of publication bias was not assessed
Randomized controlled trials (Downs and Black)		
Dal-Fabbro, ¹⁴ 2014	<ul style="list-style-type: none"> • hypothesis clearly described • patients randomized • outcome assessors were blinded to the intervention • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described 	<ul style="list-style-type: none"> • unable to determine if study power is sufficient to detect a clinically important effect • patients were not blinded to the intervention
Phillips, ¹⁵ 2013	<ul style="list-style-type: none"> • hypothesis clearly described • patients randomized • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • study power is sufficient to detect a clinically important effect • losses to follow-up described 	<ul style="list-style-type: none"> • patients and caregivers were not blinded to the intervention
Doff, ¹⁶ 2013	<ul style="list-style-type: none"> • hypothesis clearly described • patients randomized 	<ul style="list-style-type: none"> • unable to determine if study power is sufficient to detect a clinically important

Table A4: Summary of Critical Appraisal of Included Study

First Author, Publication Year	Strengths	Limitations
	<ul style="list-style-type: none"> • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described 	<ul style="list-style-type: none"> • effect • patients and caregivers were not blinded to the intervention
Cost-effectiveness studies (Drummond)		
Sadatsafavi, ¹⁷ 2009	<ul style="list-style-type: none"> • research question was stated • economic importance of the research question was stated and justified • rationale for choosing alternative programs or interventions compared was stated • details of the design and results of effectiveness studies were given • choice of form of economic evaluation was justified • sources of effectiveness estimates used were stated • an economic model was developed • sensitivity analysis was performed • details of the methods of synthesis or meta-analysis of estimates were given • primary outcome measures were clearly stated • incremental analysis was reported • methods for the estimation of quantities and unit costs were described • currency and price data were recorded • answer to the study question was given • conclusions follow from the data was reported 	<ul style="list-style-type: none"> • potential difference in costs, treatment effect and adherence of various types of oral appliances was not considered in analyses • cost data based on 1997 survey
Weatherly, ¹⁸ 2009	<ul style="list-style-type: none"> • research question was stated • economic importance of the research question was stated and justified • rationale for choosing alternative programs or interventions compared was stated • details of the design and results of effectiveness studies were given • choice of form of economic evaluation was justified • sources of effectiveness estimates used were stated • an economic model was developed • sensitivity analysis was performed • details of the methods of synthesis or meta-analysis of estimates were given • primary outcome measures were clearly stated • incremental analysis was reported • methods for the estimation of quantities and unit costs were described • currency and price data were recorded • answer to the study question was given • conclusions follow from the data was reported 	<ul style="list-style-type: none"> • potential difference in costs, treatment effect and adherence of various types of oral appliances was not considered in analyses

Appendix 4: Main Study Findings and Authors' Conclusions

Table A5: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness of continuous positive airway pressure (CPAP) compared with oral devices for the treatment of sleep apnea)		
Li, ¹² 2013	<p>Neurobehavioral and cardiovascular outcomes ESS score, health-related QoL, cognitive performance, blood pressure: similar between OA and CPAP (differences not statistically significant). Test for heterogeneity showed significant heterogeneity across cross-over trials ($P < 0.10$, $I^2 > 50\%$)</p> <p>Polysomnographic outcomes AHI: statistically significant difference between CPAP and OA in both cross-over trials (mean difference 8.25) and parallel-group trials (mean difference 5.96), in favour of CPAP. Test for heterogeneity showed significant heterogeneity across cross-over trials ($P < 0.10$, $I^2 > 50\%$)</p> <p>Arousal index, minimum S_{pO_2}, rapid eye movement sleep rate: inconsistent findings in comparing CPAP and OA efficacy among trials. Test for heterogeneity showed significant heterogeneity across cross-over trials ($P < 0.10$, $I^2 > 50\%$)</p> <p>Treatment usage, treatment preference, side effects, withdrawals Similar between OA and CPAP (differences not statistically significant). Test for heterogeneity showed substantial heterogeneity across cross-over and parallel group trials ($P < 0.10$, $I^2 > 50\%$)</p>	"CPAP yielded better polysomnography outcomes, especially in reducing AHI, than OAs...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" (p 1184)
Dal-Fabbro, ¹⁴ 2014	<p>Neurobehavioral outcomes ESS: no statistical significant difference between CPAP and MAD</p> <p>Polysomnographic outcomes Statistically significant difference between CPAP and OA, in favour of CPAP CPAP vs MAD: Stage 2 sleep % (57.4 ± 1.3 vs 63.1 ± 1.4) Arousal index (10.1 ± 0.7 vs 24.8 ± 3.9) AHI (3.2 ± 0.4 vs 26.7 ± 4.8) Supine apnea-hypopnea events (11.9 ± 1.9 vs 74.9 ± 12.1) Minimum S_{pO_2} (90.4 ± 0.5 vs 84.2 ± 1.2)</p> <p>Cardiovascular outcomes Blood pressure: similar between OA and CPAP (differences not statistically significant)</p> <p>Oxidative stress No statistical significant difference between CPAP and MAD in lipid peroxidation products, erythrocyte superoxide dismutase activity.</p> <p>Compliance rate Statistically significant difference between CPAP and OA in patients with severe OSA, in favour of MAD MAD vs CPAP</p>	"Even though CPAP proved to be more effective at attenuating OSA, better compliance with MAD..." (p 749)

Table A5: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	(86.3 ± 3.0% vs 72.0 ± 4.2%)	
Phillips, ¹⁵ 2013	<p>Neurobehavioral outcomes ESS: no statistical significant difference between CPAP and MAD QoL: statistically significant difference between CPAP and MAD in 4 general quality-of-life domains, in favour of MAD Bodily pain (mean difference -4.8; 95% CI -.87 to -0.9) Vitality (mean difference -3.8; 95% CI -7.7 to -0.02) Mental health (mean difference -2.6; 95% CI -5.1 to -0.2) Mental component (mean difference -3.5; 95% CI -6.7 to -0.3)</p> <p>Polysomnography outcomes Statistically significant difference between CPAP and MAD, in favour of CPAP CPAP vs MAD: AHI (4.5 vs 11.1) Minimum S_{PO2} (90.6 vs 87.2) Arousal index (16.6 vs 19.2) Total sleep time (6.9 vs 7.1)</p> <p>Cardiovascular outcomes Blood pressure, arterial stiffness: no statistical significant difference between CPAP and MAD</p> <p>Compliance Statistically significant difference between CPAP and MAD, in favour of MAD MAD vs CPAP: 6.5 ± 1.3 hr/night vs 5.20 ± 2 hr/night</p>	<p><i>"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"</i> (p 879)</p>
Research question 2 (clinical effectiveness of CPAP compared with lifestyle changes for the treatment of sleep apnea)		
Doff, ¹⁶ 2013	<p>Polysomnographic outcomes Except minimum S_{PO2} that favored CPAP, similar outcomes between CPAP and MAD after 2 years follow-up (differences not statistically significant)</p> <p>Neurobehavioral outcomes ESS, QoL: similar outcomes between CPAP and MAD after 2 years follow-up (differences not statistically significant)</p>	<p><i>"Oral appliances therapy should be considered as a viable treatment alternative to continuous airway pressure (CPAP) in patients with mild to moderate obstructive sleep apnea syndrome (OSAS). In patients with severe OSAP, CPAP remains the treatment of first choice."</i> (p 1289)</p>
Thomasouli, ¹³ 2013	<p>Weight reduction CPAP + diet reduced weight by -2.64 kg (95% CI -3.98 to -1.30) compared to diet alone. Test for heterogeneity showed no significant heterogeneity across trials ($P > 0.10$, $I^2 < 50\%$)</p> <p>BMI CPAP + diet reduced BMI by -0.18 kg/m² (95% CI -3.62 to -3.27) compared to diet alone. Test for heterogeneity showed significant heterogeneity across trials ($P < 0.10$, $I^2 > 50\%$)</p> <p>Neurobehavioral outcomes ESS, QoL: similar outcomes between CPAP + diet and diet alone (differences not statistically significant). Test for QoL heterogeneity showed no significant heterogeneity across</p>	<p><i>"Diet with CPAP therapy reduced weight by -2.64 kg (95 % Confidence Interval (CI) -3.98, -1.30, I²=0 %) compared with diet alone. No differences were observed for QoL or Epworth Sleepiness Scale"</i> (p 925)</p>

Table A5: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	trials ($P > 0.10$, $I^2 < 50\%$). Test for ESS showed significant heterogeneity showed significant heterogeneity across trials ($P < 0.10$, $I^2 > 50\%$)	
Research question 3 (cost-effectiveness of CPAP compared with oral devices or lifestyle changes for the treatment of sleep apnea)		
Sadatsafavi, ¹⁷ 2009	<p>Base-case analysis (costs estimates using 2004 US\$) CPAP resulted in \$1,917 more costs than OA (\$6,401 vs \$4,484) CPAP increased 0.0696 QALY compared to OA (3.4962 vs 3.4266) ICER = \$27,540/QALY compared to OA</p> <p>Sensitivity analysis CPAP was more cost effective compared to OA (ICER < \$50,000/QALY) in most scenarios, except when the gain in utility was assumed to be equal between CPAP and OA</p> <p>If adherence to OA was at least 80% and adherence to CPAP was only 70%, AO became more cost-effective.</p>	"OAs are less economically attractive than CPAP but remain a cost-effective treatment for patients who are unwilling or unable to adhere to CPAP therapy" (p 241)
Weatherly, ¹⁸ 2009	<p>Base-case analysis (cost estimates using 2005- 2006 £) CPAP resulted in higher costs compared to dental devices or lifestyle advice CPAP: £9,301 Dental devices: £8.797 Lifestyle advice: £8,140 CPAP resulted in higher QALY compared to dental devices or lifestyle advice ICER = £3,899/QALY for men and £4.335/QALY for women compared to dental devices</p> <p>Sensitivity analysis CPAP was more cost effective compared to dental devices or lifestyle advice (ICER < £20,000/QALY) in all scenarios, except in mild disease group</p>	"The model suggests that CPAP is cost-effective compared with dental devices and lifestyle advice for adults with moderate or severe symptomatic OSAHS at the cost-effectiveness thresholds used by NICE. This finding is reflected in the NICE guidance" (p 26)

AHI: Apnea-Hypopnea Index; BMI: body mass index; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; ICER: incremental cost-effectiveness ratio; OA: oral appliances; QALY: quality-adjusted life year; QoL: quality of life; minimum S_{pO_2} : minimum arterial oxygen saturation