Sleep Med Rev. Author manuscript; available in PMC 2017 April 03.

Published in final edited form as:
Sleep Med Rev. 2016 June ; 27: 108–124. doi:10.1016/j.smrv.2015.05.003.

Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea

Linda D. Sharples[a,b,*], **Abigail L. Clutterbuck-James**[c], **Matthew J. Glover**[d], **Maxine S. Bennett**[b], **Rebecca Chadwick**[e], **Marcus A. Pittman**[c], and **Timothy G. Quinnell**[c]

[a]University of Leeds Clinical Trials Research Unit, Leeds, United Kingdom

[b]Medical Research Council Biostatistics Unit, Cambridge, United Kingdom

[c]Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, United Kingdom

[d]Health Economics Research Unit, Brunel University, Uxbridge, Middlesex, United Kingdom

[e]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, United Kingdom

Summary

Obstructive sleep apnoea-hypopnoea (OSAH) causes excessive daytime sleepiness, impairs quality-of-life, and increases cardiovascular disease and road traffic accident risks. Continuous positive airway pressure (CPAP) treatment and mandibular advancement devices (MAD) have been shown to be effective in individual trials but their effectiveness particularly relative to disease severity is unclear.

A MEDLINE, Embase and Science Citation Index search updating two systematic reviews to August 2013 identified 77 RCTs in adult OSAH patients comparing: MAD with conservative management (CM); MAD with CPAP; or CPAP with CM. Overall MAD and CPAP significantly improved apnoea-hypopnoea index (AHI) (MAD −9.3/hr ($p < 0.001$), CPAP −25.4 ($p < 0.001$)). In direct comparisons mean AHI and Epworth sleepiness scale score were lower (7.0/hr ($p < 0.001$) and 0.67 ($p = 0.093$) respectively) for CPAP. There were no CPAP vs. MAD trials in mild OSAH but in comparisons with CM, MAD and CPAP reduced ESS similarly (MAD 2.01 ($p < 0.001$); CPAP 1.23 ($p = 0.012$).

*Corresponding author. Clinical Trials Research Unit, University of Leeds, Leeds, LS2 9JT, United Kingdom. Tel.: +44 (0)113 343 5616; fax: +44 (0)113 343 1471. l.sharples@leeds.ac.uk (L.D. Sharples).

Contribution of authors

Dr Timothy Quinnell was the chief investigator for the study. Prof. Linda Sharples designed the meta-analysis and had overall responsibility for research methodology. The literature searching and study identification was conducted by Dr Abigail Clutterbuck-James, Maxine Bennett, Matthew Glover, Rebecca Chadwick, Dr Marcus Pittman and the meta-analysis was conducted and interpreted by Prof. Sharples. Prof. Sharples, Dr Quinnell and Dr Clutterbuck-James created the first draft of the paper. All authors reviewed the draft and contributed to the final version.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Both MAD and CPAP are clinically effective in the treatment of OSAH. Although CPAP has a greater treatment effect, MAD is an appropriate treatment for patients who are intolerant of CPAP and may be comparable to CPAP in mild disease.

Keywords

Meta-analysis; Obstructive sleep apnoea-hypopnoea; Mandibular advancement device; Continuous positive airway pressure

Introduction

Obstructive sleep apnoea-hypopnoea (OSAH) is characterised by repeated interruption of breathing during sleep due to episodic collapse of the pharyngeal airway. These episodes usually cause oxygen desaturation and are terminated by micro-arousals from sleep. This sleep disruption commonly causes excessive daytime sleepiness (EDS) [1].

Published studies suggest that OSAH affects 2%–7% of the adult population [2]. It becomes more prevalent in middle age and males have approximately double the risk of developing the condition [3]. The main modifiable risk factor for OSAH is obesity, particularly when adiposity is distributed around the neck and upper body [4]. Others include smoking and alcohol use. Medical conditions such as hypothyroidism, polycystic ovary syndrome and acromegaly have also been associated with OSAH [2,4].

The sequelae of OSAH can be serious. There is a causal link with hypertension [5]. A recent meta-analysis estimated the risk of cardiovascular disease (CVD) to be 2.5 times higher in patients with moderate-severe OSAH [6]. This association is supported by biologically plausible mechanisms. Intermittent hypoxia, micro-arousals and excessive negative intrathoracic pressure swings may all play a role, mediated via sympathetic activation, oxidative stress and inflammation, as well as through direct cardiac effects [7]. There is also evidence for improvement in cardiovascular outcomes when OSA is treated. While the case is strongest for hypertension, there may be other cardiovascular benefits, although conclusive evidence is still needed. There are other consequences of OSAH. Impaired vigilance is responsible for a two to three fold increase in road traffic accident (RTA) risk [8], while health related quality of life (HRQoL) is also diminished [9]. Healthcare usage is almost doubled in OSAH, with one of the main determinants of increased cost being CVD [10].

The AHI is an objective, sensitive and specific measure of the severity of OSAH. It allows useful if arbitrary disease categorisation, although differing hypopnoea definitions introduce variability. The American Academy of Sleep Medicine (AASM) defines mild OSAH as an AHI of 5–14 events per hour; moderate OSAH as 15–30 events per hour; and severe OSAH as an AHI of greater than 30 events per hour [11].

Impact on excessive daytime sleepiness (EDS) is routinely measured when evaluating the effectiveness of different treatments for OSAH. The extensively validated Epworth sleepiness scale (ESS) is the most frequently used instrument [12]. As a subjective measure

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it is susceptible to significant placebo effects [13] but it has been found to be the best among a range of validated outcome measures in predicting real response to OSAH treatment [14].

For milder cases of OSAH, treatment focuses on lifestyle modification (weight loss, smoking cessation, reduction of alcohol intake, position management and sleep hygiene). When the symptoms of OSAH are more severe definitive treatment is usually recommended, most commonly CPAP. Pressure generated by an electric air pump is applied to the upper airway via a face mask. It provides a pneumatic splint which maintains pharyngeal patency during sleep. There is good evidence that CPAP reduces obstructive events and improves daytime sleepiness, cognitive function, HRQoL and CVD risk factors. However almost all trials have been conducted in patients with moderate-severe OSAH [9,15,16], and CPAP intolerance, which frequently undermines its effectiveness, may be a particular problem in milder disease [17].

Mandibular advancement devices (MAD) are an alternative to CPAP in the treatment of OSAH. Worn intraorally during sleep, they can prevent upper airway collapse by holding the mandible and tongue forward. A wide variety of devices are available, covering a range of sophistication and cost. Improvement in respiratory events has been associated with MAD-mediated increase in upper airway dimensions [18]. The positive treatment effect, coupled with compliance rates that may be higher than for CPAP, suggest MADs are an effective treatment in patients with mild to moderate OSAH.

Three meta-analyses have examined the evidence for the use of MAD in OSAH [9,15,19]. Lim et al. [19] reviewed 17 RCTs on MAD involving 831 patients. They concluded that MADs were effective in reducing AHI, ESS and other measures of sleep-disordered breathing compared with conservative management (CM), but less than CPAP. Effects on quality of life, symptoms, CVD risk factors and RTAs were unclear due to the small number of studies and inconsistent methodology. An earlier Cochrane review [15] compared CPAP to controls and MADs in separate analyses. CPAP was best at reducing AHI. However, ESS improvements were similar for CPAP and MADs, with both better than no treatment. There was evidence of greater CPAP effectiveness with increasing baseline AHI severity. McDaid et al. [9] compared CPAP with control (placebo and conservative treatment) and MAD in separate analyses. They identified 48 studies reporting at least one measure of clinical effectiveness. Twenty-nine included ESS as the primary outcome. Most studies included people with severe disease by baseline AHI. There was less evidence of a difference between CPAP and MAD impacts on ESS, compared to CPAP and control. The small number of trials directly comparing these two treatments makes it difficult to elucidate the reasons for the differing AHI and ESS effects, but others have also noted only moderate correlation between AHI and ESS [20]. In common with Lim et al., [19] results regarding quality of life and cardiovascular risks were inconclusive due to the small numbers of trials and patients, short follow up and heterogeneous outcome measures.

This meta-analysis was designed to update systematic reviews of the effects on OSAH of MAD and CPAP, compared with each other and with CM, and to estimate the effect on AHI and ESS of both treatments. This includes assessment of heterogeneity due to baseline AHI severity, baseline ESS severity, trial methodology and duration of follow up.

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Methods

Search strategy for the systematic review

The systematic review included RCTs of adult (16 y or older) OSAH patients with at least one arm randomised to MAD or CPAP. Exclusions were: studies comparing two different MAD or two different types of CPAP (differences within treatment modalities are small and numerous different devices are available), animal studies, non-randomised studies and trials published in a language other than English.

Information sources used to identify studies

The search strategy updated two existing systematic reviews [9,19] to August 2013, when the main analysis was conducted. The main stages of the search are described below.

1) All studies reported in the McDaid et al. systematic review [9] were included, which searched 14 databases up to November 2006 and included all RCTs of CPAP compared with either MAD or a non-MAD control. This search was repeated in 2012 by the authors of McDaid et al. (York University Centres for Reviews and Dissemination and for Health Economics) and results were shared with the authors of this article. This search strategy was repeated, by the authors, to retrieve articles from March 2012 to August 2013 using MEDLINE, Embase and the Science Citation Index, the three most sensitive databases reported by McDaid [9], to identify recent trials.

2) The search by McDaid et al. [9] did not include studies of MAD against CM. Therefore additional papers were identified from Lim [19], and an updated version of the Lim strategy re-run to cover the period June 2008 and August 2013, using MEDLINE, Embase and the Science Citation Index.

3) Reference lists of papers were searched and supplemented by the research team's expert knowledge of the area to identify other trials missed in updated searches.

Inclusion criteria

All studies published by McDaid et al. and Lim et al. were reviewed. For subsequent searches, titles and abstracts were screened independently for relevance by two of the authors (of MB, MG, AC-J, RC and MP). Disagreements were resolved by consensus.

Patients

Full papers were retrieved for RCTs of adult patients with newly diagnosed or existing OSAH of any severity and confirmed using an appropriate method such as polysomnography. Studies were excluded if OSAH was not the predominant diagnosis, for example sleep disordered breathing associated with heart disease, stroke or dementia.

Interventions

Trials with at least one randomised comparison of i) MAD (fixed or adjustable) against CM ii) CPAP (fixed or autotitrating) against CM, iii) MAD (fixed or adjustable) against CPAP (fixed or autotitrating) were included. CM included usual care, recommendation to lose

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weight or reduce alcohol consumption, sham device, placebo pill or postural device aimed at discouraging supine sleeping. Although data were extracted from studies where a surgical intervention was compared with either MAD or CPAP, this was not considered to be CM and the studies were excluded from the meta-analysis.

Trial methods

All trial methodologies that included randomised allocation were included. In practice, trials were either i) crossover in design, with all patients receiving at least one active treatment and the order of treatment determined at random, or ii) individually-randomised, parallel-groups trials, with each patient receiving one treatment only. Trials in which the treatment duration was ≤ one week were excluded since this period was considered inadequate to produce a treatment effect.

Outcome measurements

This review focusses on AHI and ESS, the most commonly reported outcomes used to assess treatment effectiveness.

Data extracted from published studies

For previously published reviews (see above), estimates of treatment effects recorded in the relevant papers were used after checking their accuracy in the published article or abstract [9,19]. For newly identified studies information from full papers was extracted independently by two of the authors (of MB, MG, AC-J, RC and MP) and entered onto a bespoke data extraction form. Queries were resolved by consensus. Studies available as abstracts only were included provided that we could verify the inclusion and exclusion criteria, and at least one of the outcomes of interest was reported. For the updated review of MAD, if data in the published abstract, index paper, or a related publication were unclear, the authors were approached for further information. It was not possible within the timescale of the study to pursue authors of trials involving CPAP for data that were not published in the abstract, index paper, or a related publication.

Data extracted included details of the patient sample and baseline characteristics, intervention and comparator, outcome measurements, trial methodology, treatment duration and results.

Mean differences between the groups for continuous outcomes, and standard errors of the group differences, were extracted for the meta-analysis.

Quality assessment

The Jadad score was calculated as a measure of quality for consistency with previously published reviews [9,19]. The Jadad score was calculated by one reviewer and checked by a second.

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Publication bias

Funnel plots were examined as an informal method of assessing publication bias. These showed little evidence of asymmetry but the number of studies was too small for more formal analysis.

Data analysis

Three separate meta-analyses were conducted, one for each of the comparisons i) MAD against CM, ii) MAD against CPAP and iii) CPAP against CM. Meta-analyses used random effects methods and were implemented using **metan** and related commands in STATA version 12 [21] and in WinBUGS [22]. In brief, this model was formulated as follows. From each study *i* we have an estimate of the treatment effect compared with the control treatment as $\hat{\beta}_i$ and we assume that these estimates follow a *Gaussian* distribution with

$$\hat{\beta}_i|\beta_i \sim N\left(\beta_i, \sigma_i^2\right)$$

where β_i is the underlying mean treatment effect and σ_i^2 is the standard error in trial *i*. We assume that the trials are exchangeable *a priori* and that the underlying trial parameters β_i are drawn from a *Gaussian* distribution with mean $\mu = E[\beta_i]$ and variance $\tau^2 = Var[\beta_i]$.

The methods used in STATA follow DerSimonian and Laird (1986) [21] who take a classical approach to random-effects metaanalysis. The expected treatment effect μ is estimated as the weighted average,

$$\hat{\mu}=\sum \hat{\beta}_i\hat{w}_i/\hat{w}_i$$

where the weights are given by the inverse of the estimated total variance $\hat{w}_i=1/\left(\sigma_i^2+\tau^2\right)$.

The standard error of $\hat{\mu}$ is approximated by $\sqrt{(1/\Sigma\hat{w}_i)}$ and an approximate 95% confidence interval is given by

$$\hat{\mu} \pm 1.96\sqrt{(1/\Sigma\hat{w}_i)}.$$

All outcomes were assumed to be normally distributed. The standard error term σ_i^2 was estimated by the within-trial standard error. Where only 95% confidence intervals were available the standard error was estimated using (upper limit-lower limit)/3.92.

Although we investigated combining all trial results in a formal network meta-analysis, differences in control trial samples meant that these comparisons were unsound and these results are not reported. Informal indirect comparisons are discussed.

Heterogeneity between studies was represented by the I^2 statistic and the χ^2 test for heterogeneity [23]. In order to investigate the sources of heterogeneity the combined treatment effects for AHI and ESS were re-estimated in each of the following subgroups.

1) Mean baseline AHI events/hour: mild (AHI 5–14), moderate (AHI 15–30) and severe (AHI > 30). If only mean DI, rather than mean AHI was available, severity was classified as: mild (DI 5–9), moderate (DI 10–30) and severe (DI > 30).

2) Mean baseline ESS score: normal/mild (0–9), moderate (10–15) and severe (16–24)

3) Study design: parallel and crossover

4) Treatment duration for studies involving MAD: short (2–12 wk) and long (>12 wk), and for studies of CPAP against CM: short (2–4 wk) medium (5–12 wk) and long (>12 wk)

Results

Quantity and quality of studies

Results of the literature search are summarised in Fig. 1. After combining studies identified in previous reviews which had not been superceded by subsequent reports (44 studies) with those identified in the current review (27 studies) 71 trials were included. Three studies compared MAD, CPAP and CM and so each contribute to three separate comparisons, giving a total of 77 separate comparisons [24–26]. Most studies focussed on the effectiveness of CPAP.

Summary of included studies

Summaries of the baseline characteristics for the included studies are shown in Table 1. Twelve studies (629 patients) compared MAD against CM, 13 studies (746 patients) compared MAD against CPAP and 52 studies (5400 patients) compared CPAP with CM.

Patient characteristics

As expected the study samples included a large proportion of men, ranging from 65% to 100%, median 81%. The reported mean ages ranged from 44.0 to 59.2 y. Most trial samples were over-weight or obese on average, with mean body mass index ranging from 28.3 kg/m^2 to 35.1 kg/m^2.

In general CPAP trials were conducted in patient samples with more severe AHI/ESS at baseline than were MAD trials. Of 51 CPAP-CM comparisons that recorded average baseline AHI, 35 (69%) were in patients with an average AHI greater than 30 events/hour (severe OSAH) compared with three of 12 (25%) MAD-CM trials. Only five CPAP-CM trials were in patients with mild AHI at baseline. Most MAD-CM trials (seven of 12, 58%) were in patients with moderate AHI at baseline. In trials directly comparing MAD with CPAP, one did not record baseline AHI, eight of the remaining 12 (67%) reported moderate and four (33%) reported severe average baseline AHI.

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Average baseline ESS was available for 60 comparisons. Of these, all nine MAD-CPAP trials and seven of the eight (88%) MAD-CM trials reported moderate mean baseline ESS. Of the 43 CPAP-CM comparisons, six (14%) had normal/mild, 32 (74%) had moderate and five (12%) had severe mean baseline daytime sleepiness according to ESS.

Intervention and comparators

Thirteen (53%) of 25 trials involving MAD used adjustable devices, 10 (40%) used fixed devices and two (8%) did not report the type. In 13 trials (52%) the MAD was compared directly with CPAP, nine (36%) used a sham MAD, one compared MAD with a placebo tablet, one with conservative treatment and one with no treatment.

Of 65 trials involving CPAP 54 (83%) used fixed CPAP, six (9%) autotitrating machines and five (8%) did not report this information. Excluding the 13 trials comparing CPAP with MAD, 29 of 52 (56%) compared CPAP with a sham version, seven (13%) with placebo tablet and nine (13%) with conservative management or no treatment.

Study design

Trials were almost invariably small (see Table 1). The median number of patients randomised in MAD-CM trials was 48 (range 21–91), in MAD-CPAP trials 51 (range 20–122) and in CPAP-CM 52 (range 10 to 1105). Duration of treatment was generally short, with 60 of 76 (79%) trials that reported duration having a treatment period of 12 wk or less. Nine of 13 (69%) MAD-CPAP trials had a crossover design, compared with six of 12 (50%) MAD-CM trials and 16 of 52 (31%) CPAP-CM trials.

Study quality

The Jadad score was available for 69 of the 71 trials, with average score close to three for comparisons against CM. The mean Jadad score was 2.9 in MAD-CM trials, 2.3 in MAD-CPAP comparisons and 3.1 in CPAP-CM trials, with the lower mean scores in MAD-CPAP comparisons mainly attributable to the difficulty in blinding the two active treatments.

Apnoea-hypopnoea index

MAD compared with CM—Twelve studies (629 patients) provided an estimate of the effect on AHI, but one of these [27] only provided a point estimate and could not be included in the meta-analysis (see Fig. 2). The mean difference (reduction) in AHI for MAD compared with CM was −9.29 events/hour, (95%CI −12.28, −6.30), $p < 0.001$. There was significant heterogeneity between studies ($I^2 = 60\%$, $p = 0.005$), partly arising from differences in baseline severity of AHI. Only two studies were in patients with mild OSAH and the treatment effect for these studies differed by more than nine events per hour. Six of the 11 studies had a crossover design and these studies had more heterogeneous results than parallel group trials (see Table 2). Treatment effects were greater in crossover trials than in parallel group designs, although the difference between designs was not large. In addition, treatment effects in trials of short duration were larger than in longer-term studies.

MAD compared with CPAP—From 13 trials (746 patients) the estimated overall difference in AHI was 7.03 events/hour (95%CI 5.41, 8.66), $p < 0.001$, with CPAP having

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lower post-treatment AHI than MAD (see Fig. 3). Again there was important heterogeneity between study results, with smaller studies [28–31] and shorter studies [28,29,31], estimating greater effects than larger and longer studies. No MAD-CPAP head-to-head comparisons were reported in patients with mild baseline AHI (see Table 3) and all nine trials reported moderate average ESS at baseline. Estimates of the difference in post-treatment AHI were consistent and were not related to baseline AHI (moderate compared with severe), trial design or duration of treatment, with all significantly lower, by approximately seven events per hour, after CPAP (see Table 3).

CPAP compared with CM—Of 52 CPAP-CM trials, 25 (1596 patients) reported post-treatment AHI, with combined effect of −25.37 events/hour (95% CI −30.67, −20.07), $p < 0.001$ (see Fig. 4). There was a significant amount of heterogeneity between study results, both overall and within strata. Some heterogeneity could be explained by baseline AHI severity and the potential for treatment effect is naturally governed by the extent of disease in the sample. Only one of these studies was in patients with mild baseline AHI [32] and the estimated mean effect in this trial was small at −2.40 events/hour (95% CI −3.67, −1.13). The mean difference in AHI between CPAP and CM patients increased with baseline severity, from −13.67 events/hour (95%CI −16.13, −11.20) for moderate AHI at baseline to −33.04 events/hour (95%CI −39.75, −26.34) for severe (see Table 4). One trial reported normal/mild ESS at baseline but, despite this, baseline AHI was severe and the treatment effect was large. With the exception of this study the effect of CPAP on AHI was related to baseline ESS severity. There was some evidence that the treatment was less effective in crossover trials compared with parallel group trials. In common with MAD-CM comparisons, trials with longer treatment duration had lower treatment effects than shorter trials (see Table 4).

Epworth sleepiness scale

MAD compared with CM—Ten studies reported a point estimate for ESS but only nine reported the standard error of the treatment effect and so could be included in the meta-analysis. For these nine studies (485 patients) the combined treatment effect on ESS was −1.64 (−2.46, −0.82) (see Fig. 5 and Table 5). There was significant heterogeneity, with small studies [33,34] more likely to report large treatment differences (see Fig. 5). One study was conducted in patients with mild AHI at baseline and the effect on ESS in this study was between, and of a similar order to, estimates from trials in patient populations with moderate and severe baseline AHI [35]. Due to the small number of trials and the large influence of the Blanco et al. [34] study it was not possible to reliably assess reasons for heterogeneity.

MAD compared with CPAP—Of the 12 studies directly comparing MAD and CPAP 10 trials (675 patients) recorded ESS with a combined effect of 0.67 (95%CI −0.11, 1.44), $p = 0.093$ (see Fig. 6). The positive estimate indicates that the post-treatment ESS was lower (better) in the CPAP group. There was less between-study heterogeneity in this analysis and results of stratified analysis show that any treatment effect was small, with clinically significant differences only likely for those with severe baseline AHI (see Table 6). However the number and size of trials made reliable conclusions impossible, particularly regarding mild OSAH.

CPAP compared with CM—Thirty-eight of the 52 CPAP-CM trials (4894 patients) reported the estimated post-treatment effect on ESS. These trials were plotted in Fig. 7 with combined treatment effect of −2.23 (95% CI −2.76, −1.71), $p < 0.001$. Again there was significant heterogeneity, and some stratified analyses were reported in Table 7. In common with AHI the effect of CPAP on ESS increased with baseline AHI severity, from −1.23 (95%CI −2.19, −0.27) for the mild group to −2.64 (95%CI −3.44, −1.84) for the severe group. One study did not report baseline AHI. Trial design had less impact on outcomes but longer duration of treatment was associated with decreasing treatment effect, which again mirrors the analysis of AHI.

Discussion

Our study was based on a systematic review of the available literature and robust, prospective design. The updated meta-analyses offer stronger insights into the relative effectiveness of MAD and CPAP in patients with mild-moderate OSAH. In addition the effects of baseline severity have been highlighted and used to explain some of the differences in effects between MAD and CPAP.

The three pairwise meta-analyses have shown that MAD results in a significant improvement in post-treatment AHI, and that the estimate of effect was similar irrespective of baseline AHI. CPAP produces an improvement of approximately three times that of the combined estimate for MAD. However, the majority of trials involving CPAP focus on patients with severe baseline AHI and there was strong evidence that the treatment effect, compared with CM, was related to baseline AHI severity, which is natural since a higher baseline allows greater scope for an absolute decrease. In trials directly comparing MAD with CPAP the combined estimates favour CPAP but the absolute difference between them was of the order of seven events per hour, much less than suggested by indirectly comparing MAD-CM and CPAP-CM trials. In the few trials of patients with mild baseline AHI, compared with CM the estimated reduction in AHI due to CPAP was −2.4 events/hour (95%CI −1.13, −3.67) and due to MAD was −7.79 events/hour (95%CI −16.38, 0.79). Moreover, there were no MAD-CPAP trials conducted in patients with mild average baseline AHI. This evidence suggests that CPAP results in greater overall effect on post-treatment AHI but the improvement over MAD will be lower in mild disease.

The effect of MAD on subjective daytime sleepiness measured using the ESS followed a similar pattern but this instrument was less sensitive to differences than AHI, so that differences in treatment effects between MAD and CPAP were smaller and not significant in direct comparisons. From trials of CPAP against CM the estimated effects were related to baseline EDS severity with treatment effects (95%CI) on ESS of −0.83 (−1.16, −0.51) for normal/mild, −2.19 (−2.84, 1.53) for moderate and −4.99 (−6.51, −3.47) for severe baseline ESS. This relationship between baseline severity and effect on ESS was also observed when severity was classified by average baseline AHI. When trials of similar baseline characteristics were compared there was little difference between the effects of MAD and CPAP on post-treatment ESS when assessed against CM, and this was reinforced by the results from head-to-head trials. In the few trials conducted in patients with mild baseline

AHI, compared with CM the estimated reduction in ESS due to CPAP was −1.23 (95%CI −2.19, −0.27) and due to MAD was −2.01 (95% CI −2.70, −1.32).

There was some evidence that treatment effects were stronger in trials of short duration of treatment, which may have a number of causes. CPAP is intrusive, requiring patients to wear a face mask during sleep, and there is evidence for a tailing-off of compliance over time [17]. Although there is some evidence that MAD may be better tolerated than CPAP in the short term [36–38], the limited longer-term data available suggest that compliance with this less intrusive intervention also diminishes with time [39,40]. For both active treatments progression of the underlying OSAH may mean that treatment effects decreased over time. Possible candidate mechanisms would be ageing and weight gain. Age effects would not be expected to manifest over the relatively short periods that trials run [41,42]. The evidence for CPAP use being associated with weight gain remains unclear but even when demonstrated the degree of increase seems too small to impact significantly on treated OSAH [43]. In any case, the range of trial durations in this meta-analysis was narrow, and there were too few trials (and patients) to examine this observation in detail. Further trials and, more importantly, availability of individual patient data from all trials, would allow indepth examination of the characteristics of patients that determine outcomes.

In almost all comparisons there was significant heterogeneity between trials. Although some of this could be explained by disease severity, design and treatment duration, unexplained heterogeneity remains. Although we used random-effects meta-analysis to provide unbiased point estimates and robust estimates of precision, further elucidation of the sources of heterogeneity would be useful. Routine release of anonymised, individual patient data after trials have been reported would allow greater exploration of the variation in treatment outcomes. We strongly support initiatives such as the Farr Institute in making such data freely available.

Limitations

In the meta-analysis we considered all MAD as a single treatment modality. There were too few studies to allow robust subgroup analyses and so we were unable to identify the more modest differences in effects between different MAD. It has been suggested that future meta-analyses distinguish between trials of non-adjustable MAD and those using adjustable MAD (aMAD) [44]. From the 2006 Cochrane analysis that included only trials comparing CPAP with aMAD, the ESS effect size was in favour of MAD, but not significantly [15]. We considered performing a similar subgroup analysis when updating the meta-analysis. However, device adjustability could not always be determined [31,45]. In any case, to subdivide along these lines may be too simplistic. For example, one trial with relatively weak treatment effects has previously been excluded from aMAD reviews, as they used two non-adjustable MAD [46]. However they performed ‘pseudotitration’ by adapting devices to optimise comfort and benefits, and reported near maximal (80%) jaw protrusion. Meanwhile the potential advantage of titratable aMAD has sometimes been negated by the use of uniform protrusion for all patients [30].

Three separate meta-analyses were conducted comparing MAD against CM, MAD against CPAP and CPAP against CM. A more sophisticated analysis would combine the studies into

a formal network meta-analysis, thereby adding strength to all comparisons and better aligning the studies. Whilst this method was investigated, such analyses rely on the assumption of common control populations (the associative law), which was unlikely to be true in this case, given the greater severity of OSAH in samples undergoing trials of CPAP. Furthermore the heterogeneity observed between studies suggested that combining results within and across different treatments may not be sensible. The likely implication of doing separate meta-analyses would be a loss of precision.

CM encompassed a wide range of control treatments so that their influence on the trial-based treatment effects was difficult to estimate with any precision.

In our systematic review we used the Jadad score as a measure of study quality which is rather an insensitive tool. It did, however, provide a broad structure for summarising design features reported in existing clinical trials.

We restricted this analysis to the two most frequently used outcome measures in RCTs of OSA treatment and in clinical practice. Other important clinical outcomes, such as hypertension, were not always available in published studies, and when they were the specific measurement reported was not consistent. In addition, a wide range of quality of life instruments have been used and robust meta-analysis of these outcomes has not been possible.

Where there was uncertainty regarding published evidence we were able to contact authors of trials of MAD but, due to the much larger number of studies, this was not possible for CPAP trials. However this mainly applied to trials that were only published in abstract form and is not likely to have introduced important bias.

Conclusions

For patients with moderate to severe OSAH treatment with CPAP was the most clinically-effective approach to reduction in the AHI. For individual patients who are intolerant of CPAP, treatment with a MAD may also be effective in reducing the AHI compared with no treatment. Both treatments were effective in reducing ESS, with CPAP having only a small, additional effect over MADs. In the few trials of patients with mild OSAH, CPAP and MAD were similarly effective treatment options and there was little to choose between them in terms of clinical-effectiveness. There was significant heterogeneity between patients in response to treatment, some of which could be explained by severity of OSAH at baseline (differences in the effect sizes for CPAP and MAD increased with baseline severity) and duration of treatment. Furthermore, there is unavoidable overlap between the arbitrarily defined severity groups, which introduces ambiguity. However, reliable stratification of patients for management will only be possible if anonymised individual patient data from these studies can be made available.

Acknowledgements

We would like to thank Isla Kuhn from the University of Cambridge Medical Library for her searches of the literature.

The authors have received a grant from National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 08/110/03) for a trial of mandibular advancement devices (TOMADO) (ISRCTN02309506) which will be published in full in the Journal of Health Technology Assessment. Maxine Benefit was funded by a National Institute of Health Research, Clinical Trials Methodology fellowship.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnoea–hypopnoea index
aMAD	adjustable mandibular advancement device
CI	confidence interval
CM	conservative management
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
DI	desaturation index
EDS	excessive daytime sleepiness
ES	effect size
ESS	Epworth sleepiness scale
HRQoL	health-related quality of life
ID	identification
MAD	mandibular advancement device
OSAH	obstructive sleep apnoea–hypopnoea
RCT	randomised controlled trial
RTA	road traffic accident

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Practice points

This meta-analysis shows that:

1. CPAP is the most clinically effective treatment at reducing AHI in moderate to severe OSAH.
2. Both CPAP and MAD reduce subjective sleepiness to a similar extent in OSAHS.
3. MAD are better than no treatment for CPAP-intolerant patients and, based on indirect comparisons, may be as effective as CPAP in mild disease.

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Research agenda

Future research needs to address:

1. whether adjustable MAD offer additional benefits in terms of treatment outcomes over non-titratable devices, using prospective head-to-head trials.
2. using evidence obtained from (1) the comparative effectiveness of optimal MAD therapy and CPAP in mild OSAHS.
3. the need for reliable stratification of patients for management using data from existing studies.
4. the need to continue to explore the effectiveness and costs of clinical strategies to predict individual patients' responses to MAD, to refine treatment choice and effectiveness in OSAHS.

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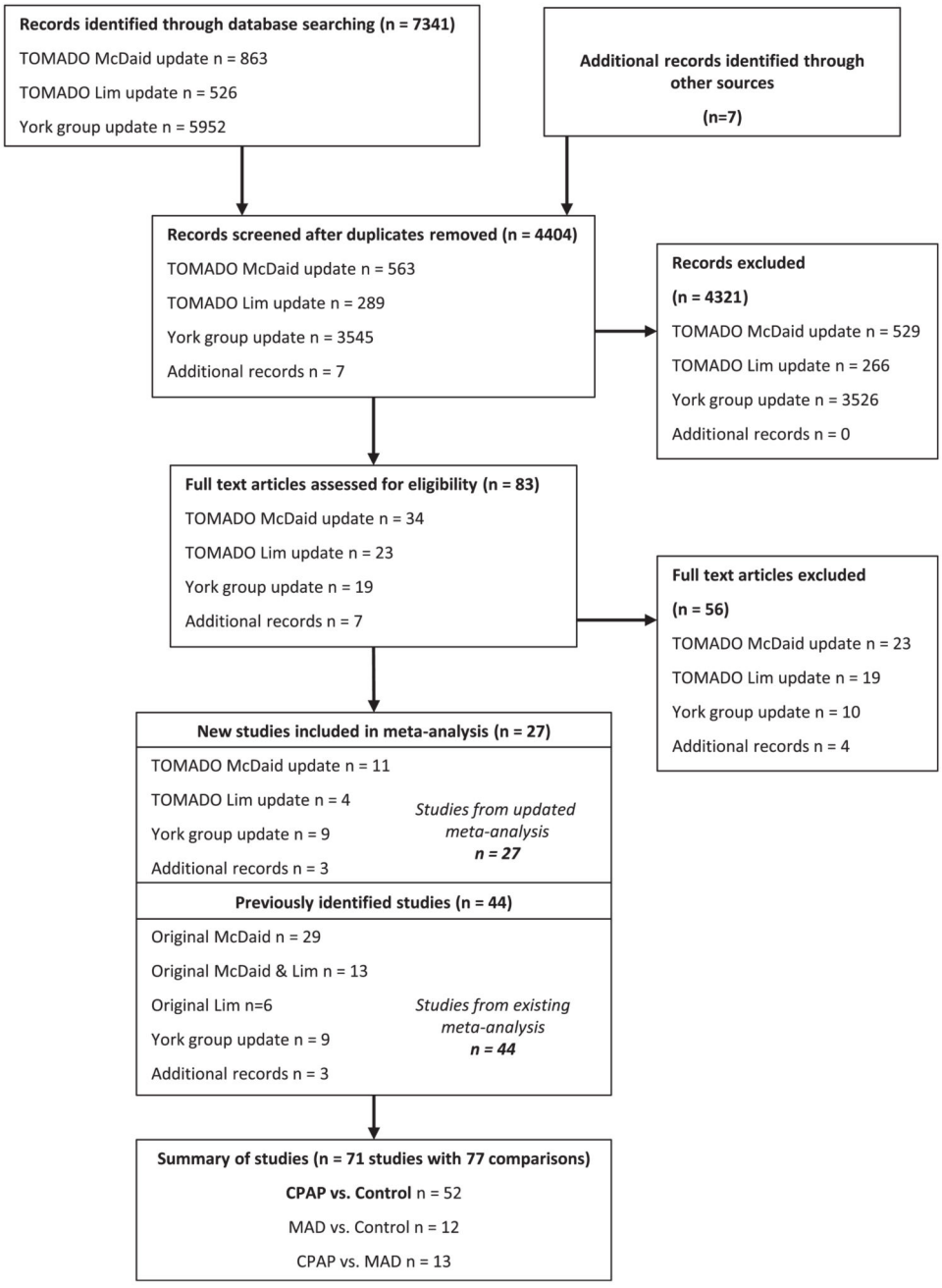

Fig. 1.

Results of the literature search. Abbreviations: CPAP: continuous positive airway pressure; MAD: mandibular advancement device; TOMADO: trial of oral mandibular advanacement devices for obstructive sleep apnoea.

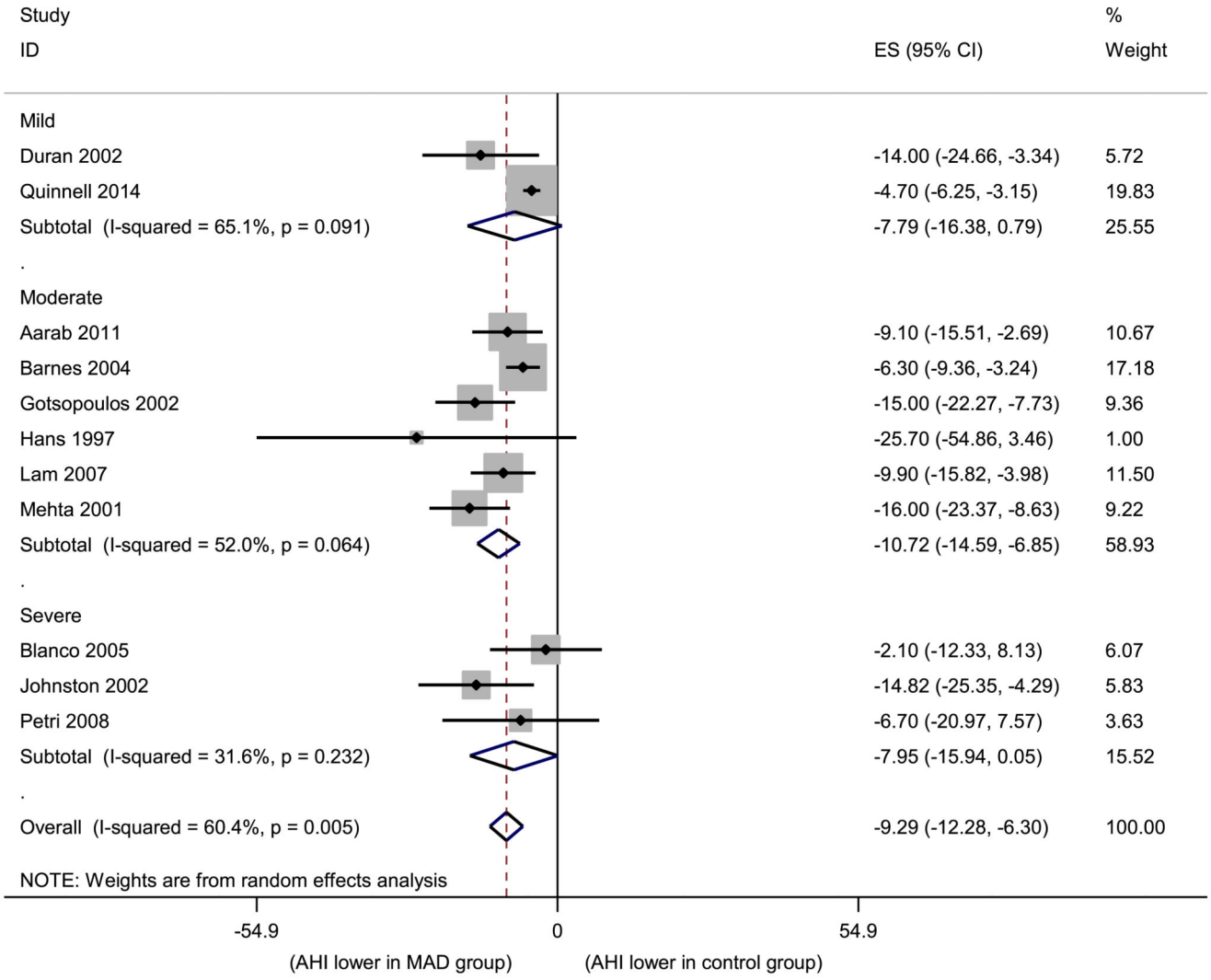

Fig. 2.

Meta-analysis of AHI results from trials of MAD compared with conservative management, stratified by baseline AHI. Mean baseline AHI/DI (events/hour); mild (AHI 5–14, DI 5–9) moderate (AHI 15–30 DI 10–30) severe (AHI > 30 DI > 30). Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; continuous positive airway pressure (CPAP); DI: desaturation index; ES: effect size; ID: identification; MAD: mandibular advancement device.

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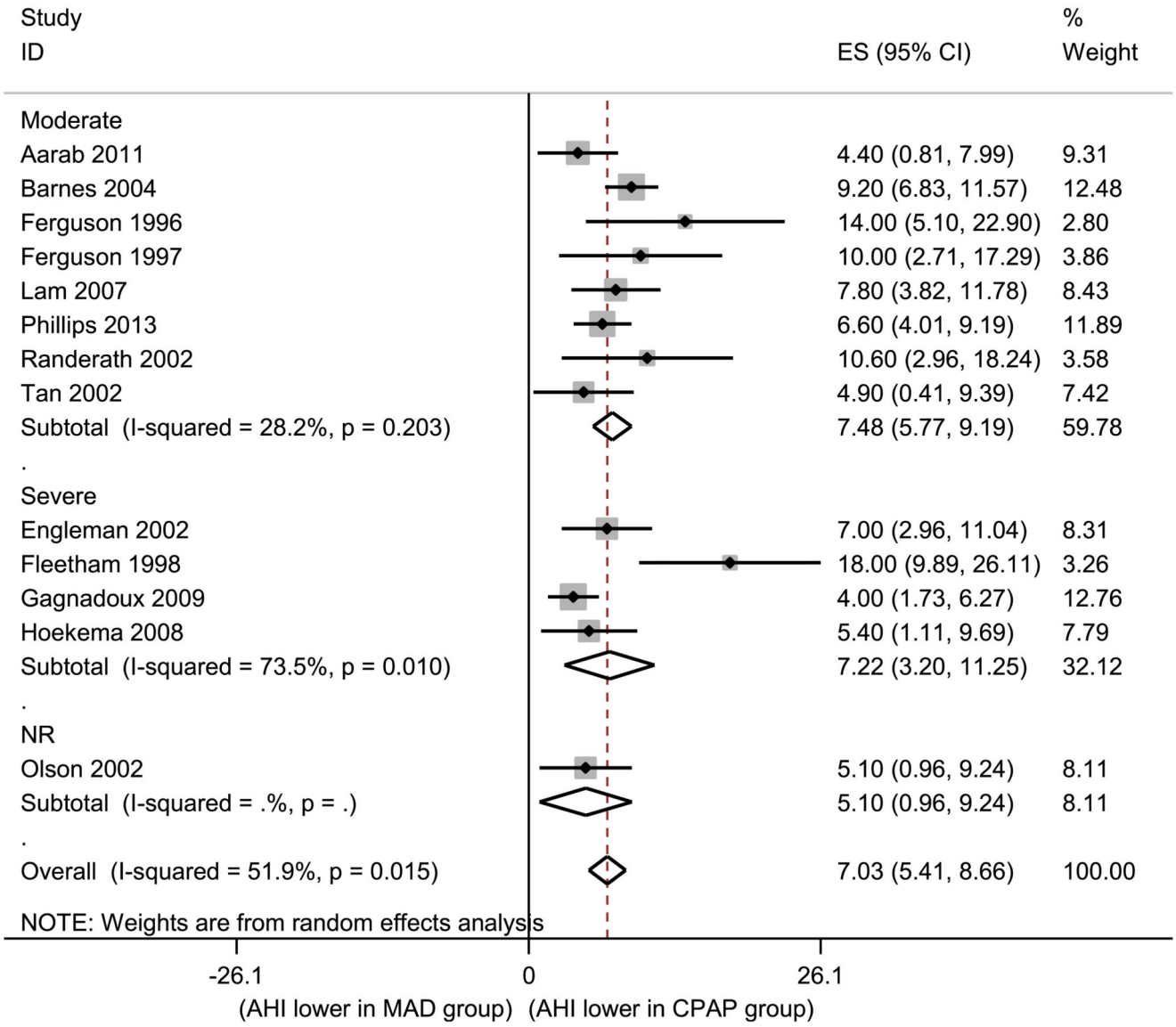

Fig. 3.

Meta-analysis of AHI results from trials of MAD compared with CPAP. Mean baseline AHI/DI (events/hour): mild (AHI 5–14, DI 5–9), moderate (AHI 15–30 DI 10–30) and severe (AHI > 30 DI > 30). Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; ES: effect size; ID: Identification; MAD: mandibular advancement device; NR: baseline AHI not recorded.

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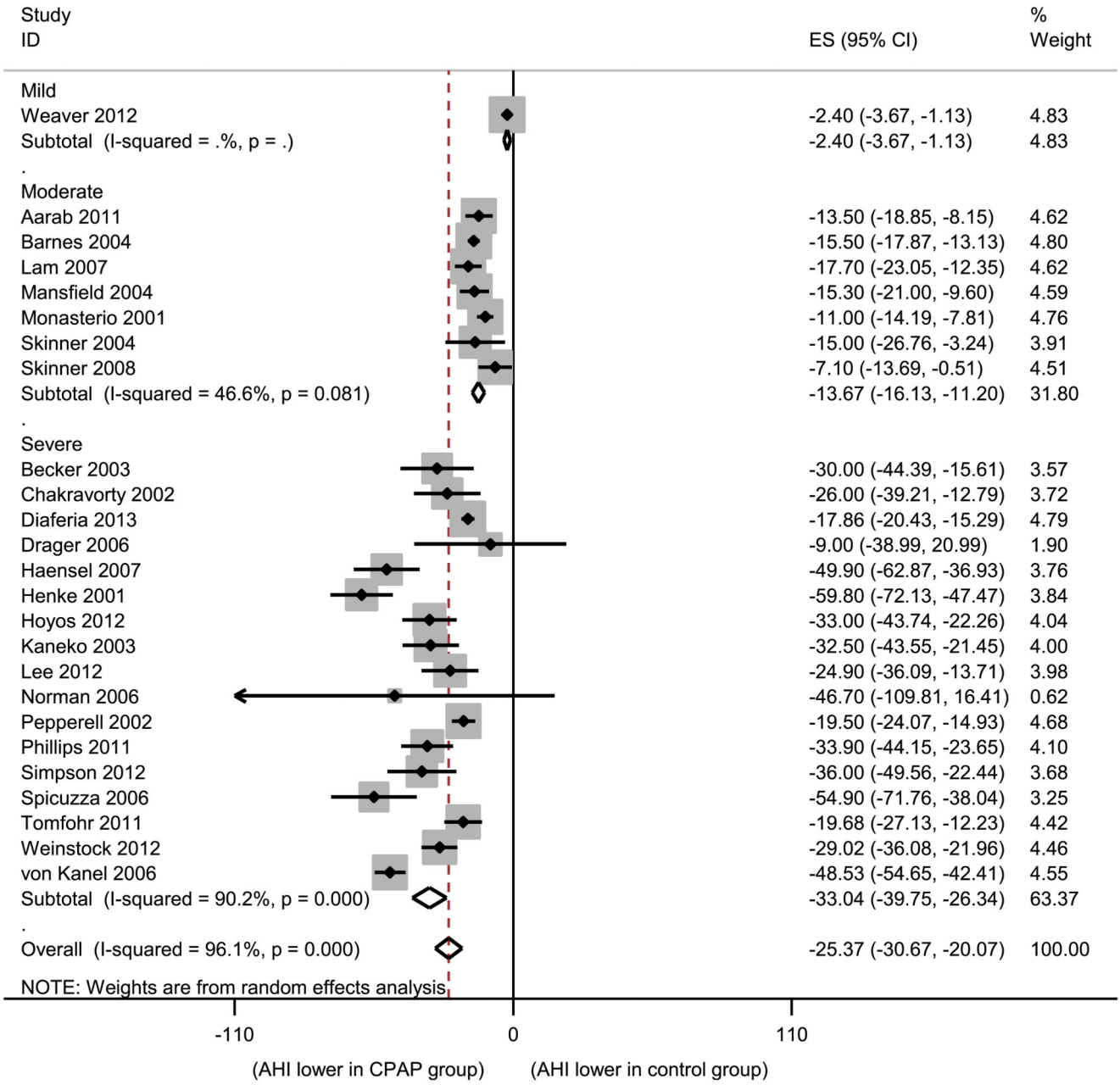

Fig. 4.

Meta-analysis of AHI results from trials of CPAP compared with conservative management, stratified by baseline AHI. Mean baseline AHI/DI (events/hour): mild (AHI 5–14, DI 5–9), moderate (AHI 15–30 DI 10–30) and severe (AHI > 30 DI > 30). Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; ES: effect size; ID: identification.

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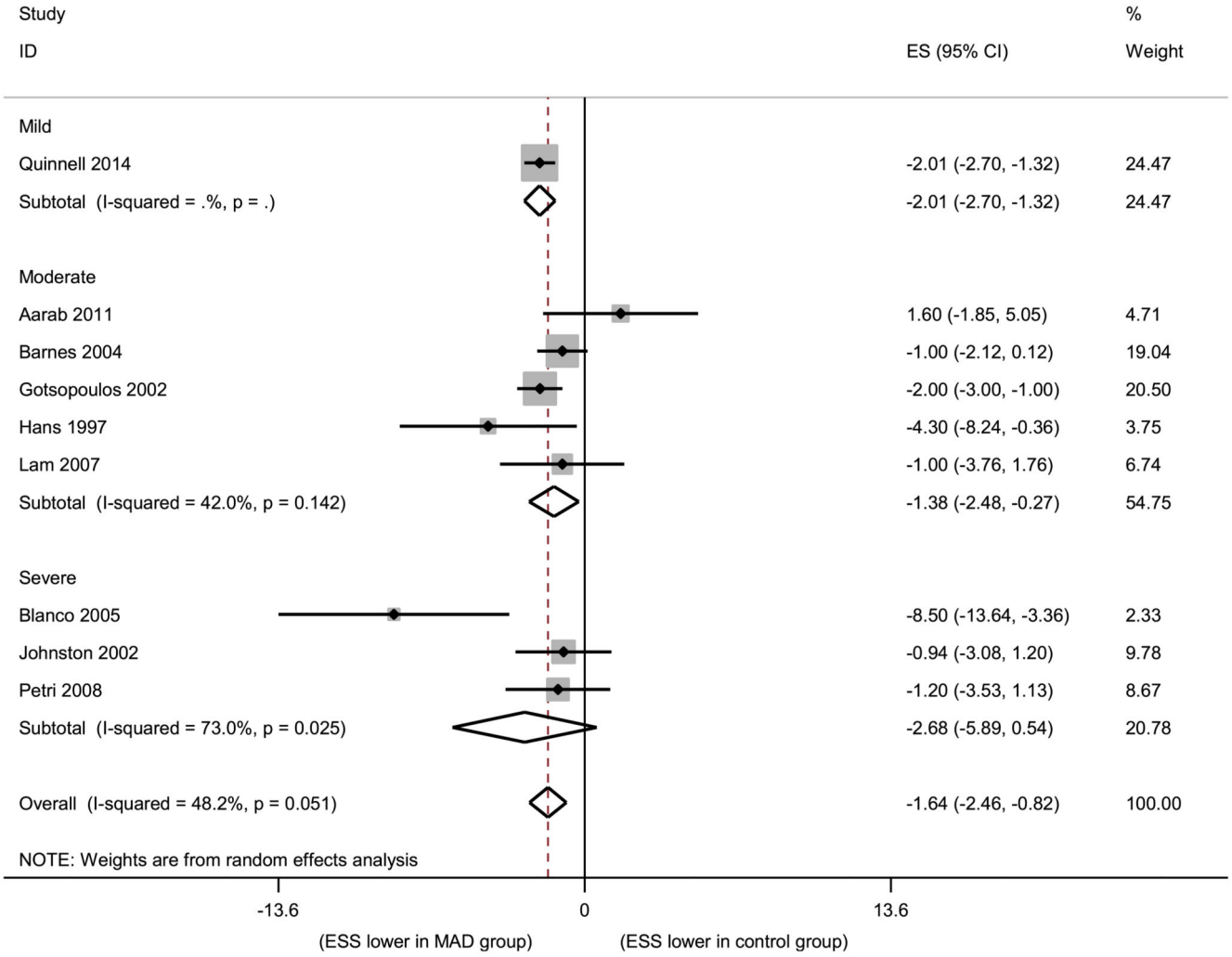

Fig. 5.

Meta-analysis of ESS results from trials of MAD compared with conservative management, stratified by baseline AHI. Mean baseline Apnoea-Hypopnoea Index/Desaturation Index (AHI/DI) events/hour: mild (AHI 5–14, DI 5–9) moderate (AHI 15–30 DI 10–30) severe (AHI > 30 DI > 30). Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; DI: desaturation index; ES: effect size; ESS: Epworth Sleepiness Scale; ID: identification; MAD: mandibular advancement device.

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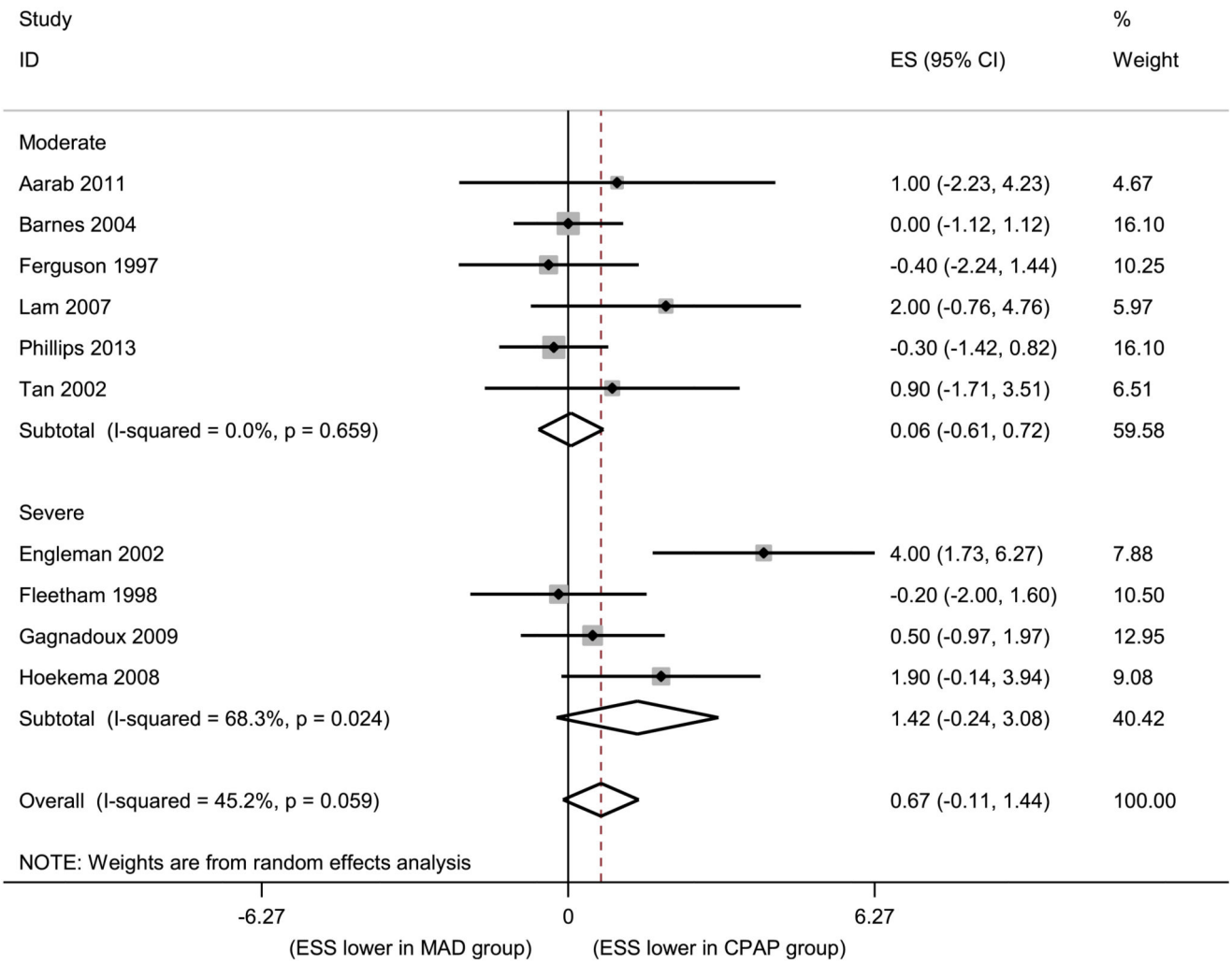

Fig. 6.

Meta-analysis of ESS results from trials of MAD compared with CPAP, stratified by baseline AHI. Mean baseline AHI/DI (events/hour): mild (AHI 5–14, DI 5–9), moderate (AHI 15–30 DI 10–30) and severe (AHI > 30 DI > 30). Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; ES: effect size; ESS: Epworth Sleepiness Scale; ID: identification; MAD: mandibular advancement device.

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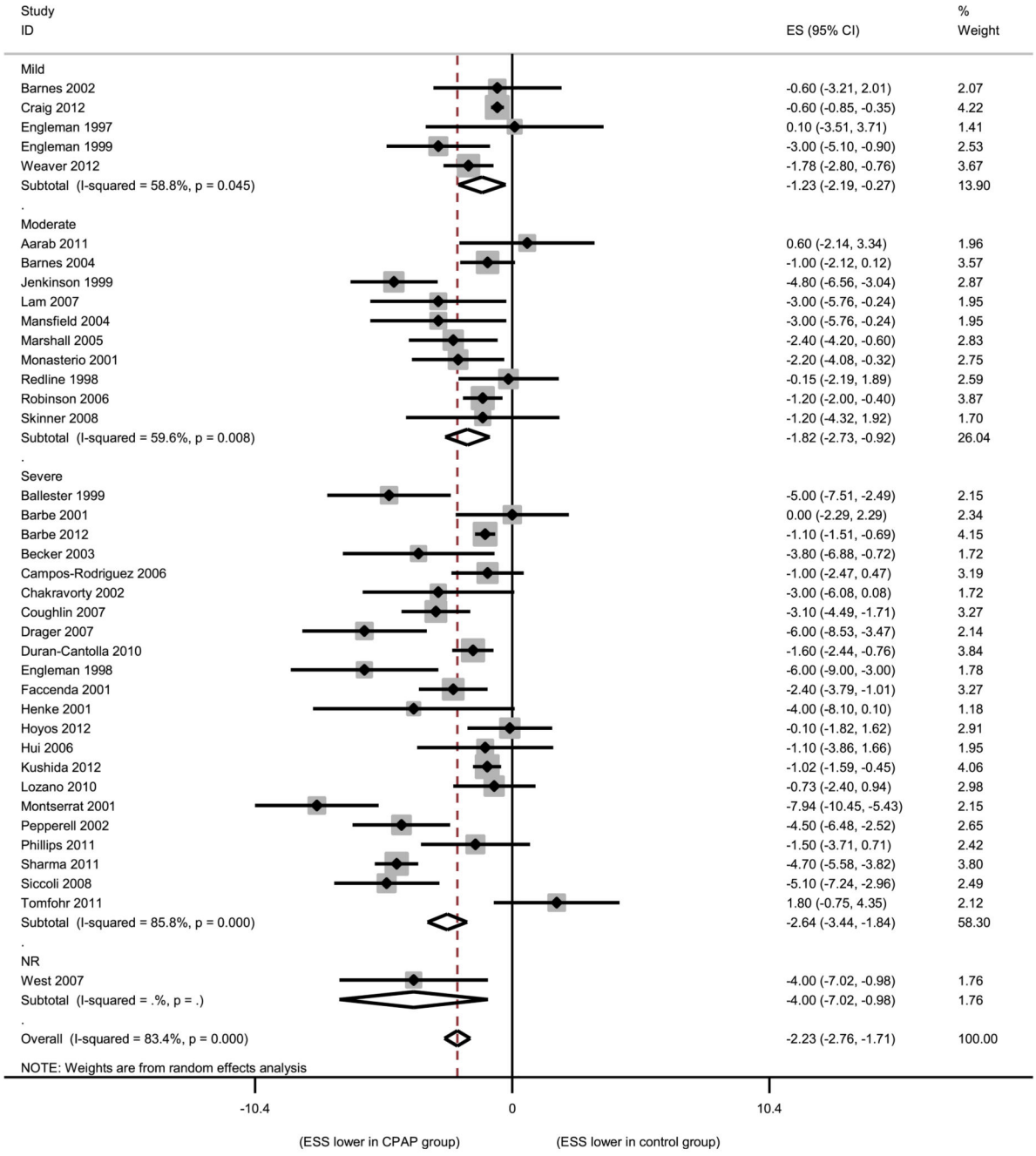

Fig. 7.

Meta-analysis of ESS results from trials of CPAP compared with conservative management. Mean baseline AHI/DI (events/hour): mild (AHI 5–14, DI 5–9), moderate (AHI 15–30 DI 10–30) and severe (AHI > 30 DI > 30). Abbreviations: apnoea-hypopnoea index (AHI); confidence interval (CI); continuous positive airway pressure (CPAP); desaturation index (DI); effect size (ES); Epworth sleepiness scale (ESS); identification (ID); baseline AHI not recorded (NR).

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Table 1

Baseline characteristics of patients and study designs for randomised controlled trials.

Study	Design	Number randomised (analysed)	Baseline severity (AHI or DI)	Baseline symptom severity (ESS)	Duration of each treatment (weeks)
MAD compared with CM					
Aarab et al. 2011 [26]	P	42	Moderate	Moderate	26
Andren et al. 2013 [27]	P	72	Moderate	Moderate	13
Barnes et al. 2004 [24]	C	80	Moderate	Moderate	12
Blanco et al. 2005 [34]	P	24 (15)	Severe	Severe	13
Duran et al. 2002 [47]	C	44 (38)	Mild	NR	NR
Gotsopoulos et al. 2002 [48]	C	85 (73)	Moderate	NR	4
Hans et al. 1997 [33]	P	24	Moderate	NR	NR
Johnston et al. 2002 [49]	C	21 (18)	Severe	Moderate	4–6
Lam et al. 2007 [25]	P	67	Moderate	Moderate	10
Mehta et al. 2001 [50]	C	28	Moderate	NR	3
Petri et al. 2008 [51]	P	52	Severe	Moderate	4
Quinnell et al. 2014 [35]	P	90	Mild	Moderate	4
MAD compared with CPAP					
Aarab et al. 2011 [26]	P	43	Moderate	Moderate	26
Barnes et al. 2004 [24]	C	80	Moderate	Moderate	12
Engelman et al. 2002 [46]	C	51 (48)	Severe	Moderate	8
Ferguson et al. 1996 [29]	C	27	Moderate	NR	17
Ferguson et al. 1997 [28]	C	24 (19)	Moderate	NR	17
Fleetham et al. 1998 [31]	P	101	Severe	Moderate	12
Hoekema et al. 2008 [52]	P	103	Severe	Moderate	8
Gagnadoux et al. 2009 [53]	C	59	Severe	Moderate	8
Lam et al. 2007 [25]	P	68	Moderate	Moderate	10
Olson et al. 2002 [45]	C	24	NR	NR	14
Phillips et al. 2013 [36]	C	122	Moderate	Moderate	4
Randerath et al. 2002 [30]	C	20	Moderate	NR	6
Tan et al. 2002 [54]	C	24 (21)	Moderate	Moderate	8
CPAP compared with CM					
Aarab et al. 2011 [26]	P	43	Moderate	Moderate	26
Arias et al. 2005 [55]	C	27	Severe	NR	12
Arias et al. 2006 [56]	P	23	Severe	NR	12
Ballester et al. 1999 [57]	P	105	Severe	Moderate	12
Barbe et al. 2001 [58]	P	55	Severe	Normal/Mild	6
Barbe et al. 2012 [59]	P	725	Severe	Normal/Mild	156
Barnes et al. 2002 [60]	C	42	Mild	Moderate	8
Barnes et al. 2004 [24]	C	80	Moderate	Moderate	12
Becker et al. 2003 [61]	P	60	Severe	Moderate	9
Campos-Rodriguez et al. 2006 [62]	P	72	Severe	Moderate	4

Study	Design	Number randomised (analysed)	Baseline severity (AHI or DI)	Baseline symptom severity (ESS)	Duration of each treatment (weeks)
Chakravorty et al. 2002 [63]	P	71	Severe	Severe	12
Coughlin et al. 2007 [64]	C	35	Severe	Moderate	6
Craig et al. 2012 [65]	P	391	Mild	Normal/Mild	26
Diafera et al. 2013 [66]	P	100	Severe	Moderate	13
Drager et al. 2006 [67]	P	16	Severe	NR	12
Drager et al. 2007 [68]	P	24	Severe	Moderate	17
Duran-Cantolla et al. 2010 [69]	P	340	Severe	Moderate	12
Engleman et al. 1996 [70]	C	16	Severe	NR	3
Engleman et al. 1997 [71]	C	18	Mild	Moderate	4
Engleman et al. 1998 [72]	C	23	Severe	Moderate	4
Engleman et al. 1999 [73]	C	37	Mild	Moderate	4
Faccenda et al. 2001 [74]	C	71	Severe	Moderate	4
Haensel et al. 2007 [75]	P	50	Severe	NR	2
Henke et al. 2001 [76]	P	45	Severe	Severe	2
Hoyos et al. 2012 [77]	P	65	Severe	Moderate	12
Hui et al. 2006 [78]	P	56	Severe	Moderate	12
Jenkinson et al. 1999 [79]	P	107	Moderate	Severe	4
Kaneko et al. 2003 [80]	P	21	Severe	Normal/Mild	4
Kushida et al. 2012 [81]	P	1105	Severe	Moderate	26
Lam et al. 2007 [25]	P	67	Moderate	Moderate	10
Lee et al. 2012 [82]	P	71	Severe	Moderate	3
Lozano et al. 2010 [83]	P	75	Severe	Normal/Mild	13
Mansfield et al. 2004 [84]	P	55	Moderate	Moderate	12
Marshall et al. 2005 [85]	C	31	Moderate	Moderate	3
Monasterio et al. 2001 [86]	P	142	Moderate	Moderate	24
Montserrat et al. 2001 [87]	P	46	Severe	Severe	6
Norman et al. 2006 [88]	P	33	Severe	Moderate	2
Pepperell et al. 2002 [16]	P	118	Severe	Severe	4
Phillips et al. 2011 [89]	C	20	Severe	Moderate	8
Redline et al. 1998 [90]	P	111	Moderate	Moderate	8
Robinson et al. 2006 [91]	C	35	Moderate	Normal/Mild	4
Sharma et al. 2011 [92]	C	90	Severe	Moderate	13
Siccoli et al. 2008 [14]	P	102	Severe	Moderate	4
Simpson et al. 2012 [93]	P	36	Severe	NR	12
Skinner et al. 2004 [94]	C	10	Moderate	Moderate	4
Skinner et al. 2008 [95]	C	20	Moderate	Moderate	4
Spicuzza et al. 2006 [96]	P	25	Severe	NR	4
Tomfohr et al. 2011 [97]	P	71	Severe	Moderate	3
Von Kanel et al. 2006 [98]	P	28	Severe	NR	2
Weaver et al. 2012 [32]	P	281	Mild	Moderate	8
Weinstock et al. 2012 [99]	C	50	Severe	NR	8

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Study	Design	Number randomised (analysed)	Baseline severity (AHI or DI)	Baseline symptom severity (ESS)	Duration of each treatment (weeks)
West et al. 2007 [100]	P	42	NR	Moderate	12

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).

Mean baseline ESS 0–9 (normal/mild) 10–15 (moderate) 16–24 (severe).

Abbreviations: apnoea-hypopnoea index (AHI); CPAP: continuous positive airway pressure; C: Crossover; DI: desaturation index; ESS: Epworth Sleepiness Score; MAD: mandibular advancement device; NR: not recorded or unclear; P: parallel.

Table 2

Subgroup analysis of AHI results (events per hour) for comparisons of MAD against conservative management (negative estimates favour MAD).

Subgroup	Number of studies	Difference in AHI: MAD-control (95%CI)	P value for effect	I^2	Heterogeneity P value
Baseline AHI					
Mild [35,47]	2	−7.79 (−16.38, 0.79)	0.075	65%	0.091
Moderate [24–26,33,48,50]	6	−10.72 (−14.59, −6.85)	<0.001	52%	0.064
Severe [24,49,51]	3	−7.95 (−15.94, 0.05)	0.051	32%	0.232
Baseline ESS					
Moderate [24–26,35,49,51]	6	−6.69 (−8.98, −4.41)	<0.001	35%	0.177
Severe [34]	1	−2.10 (−12.33, 8.13)	0.687	–	–
Trial design					
Crossover [24,35,47–50]	6	−10.17 (−14.27, −6.07)	<0.001	76%	0.001
Parallel [25,26,33,34,51]	5	−8.57 (−12.39, −4.75)	<0.001	0%	0.533
Duration of treatment					
2–12 wk [24,25,33,35,48–51]	8	−9.69 (−13.27, −6.12)	<0.001	68%	0.003
>12 wk [26,34]	2	−6.78 (−13.24, −0.33)	0.039	23%	0.56
Overall MAD compared with control					
Overall	11	−9.29 (−12.28, −6.30)	<0.001	60%	0.005

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).

Mean baseline ESS score: normal/mild (0–9), moderate (10–15) and severe (16–24).

Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; DI: desaturation index; I^2: proportion of total variability explained by heterogeneity; MAD: mandibular advancement device.

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Table 3

Subgroup analysis of AHI results (events per hour) for comparison of MAD against CPAP (positive estimates favour CPAP).

Subgroup	Number of studies	Difference in AHI: MAD-CPAP (95%CI)	P value for effect	I^2	Heterogeneity P value
Baseline AHI (1 study did not record baseline AHI)					
Moderate [24–26,28–30,36,54]	8	7.48 (5.77, 9.19)	<0.001	28%	0.203
Severe [31,46,52,53]	4	7.22 (3.20, 11.25)	<0.001	74%	0.010
Baseline ESS					
Moderate [24–26,31,36,46,52–54]	9	6.70 (4.86, 8.54)	<0.001	57%	0.098
Trial design					
Crossover [24,28–30,36,45,46,53,54]	9	6.91 (5.11, 8.71)	<0.001	48%	0.054
Parallel [25,26,31,52]	4	7.72 (3.58, 11.87)	<0.001	69%	0.022
Duration of treatment					
2–12 wk [24,25,30,31,36,46,52–54]	9	7.19 (5.25, 9.12)	<0.001	59%	0.013
>12 wk [26,28,29,45]	4	6.78 (3.25, 10.31)	<0.001	42%	0.157
Overall MAD compared with CPAP					
Overall	13	7.03 (5.41, 8.66)	<0.001	52%	0.015

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).

Mean baseline ESS score: normal/mild (0–9), moderate (10–15) and severe (16–24).

Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; I^2: proportion of total variability explained by heterogeneity; MAD: mandibular advancement device.

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Table 4

Subgroup analysis of AHI results (events/hour) for comparison of CPAP against conservative management (negative estimates favour CPAP).

Subgroup	Number of studies	Difference in AHI: CPAP-control (95%CI)	P value for effect	I^2	Heterogeneity P value
Baseline AHI					
Mild [32]	1	−2.40 (−3.67, −1.13)	<0.001	–	–
Moderate [24–26,84,86,94,95]	7	−13.67 (−16.13, −11.20)	<0.001	47%	0.081
Severe [16,61,63,66,67,75–77,80,82,88,89,93,96–99]	17	−33.04 (−39.75, −26.34)	<0.001	90%	<0.001
Baseline ESS					
Normal/Mild [80]	1	−32.50 (−43.55, −21.45)	<0.001	–	–
Moderate [24–26,32,61,66,77,82,84,86,88,89,94,95,97]	15	−17.54 (−22.51, −12.56)	<0.001	95%	<0.001
Severe [16,63,76]	3	−34.73 (−58.90, −10.57)	0.005	95%	<0.001
Trial design					
Crossover [24,89,94,95,99]	5	−19.71 (−27.95, −11.48)	<0.001	87%	<0.001
Parallel [16,25,26,32,61,63,66,67,75–77,80,82,84,86,88,93,96–98]	20	−27.08 (−33.68, −20.48)	<0.001	97%	<0.001
Duration of treatment					
2–4 wk [16,75,76,80,82,88,94–98]	11	−32.90 (−43.78, −22.02)	<0.001	93%	<0.001
5–12 wk [24,25,32,61,63,67,77,84,89,93,99]	11	−22.34 (−29.84, −14.85)	<0.001	96%	<0.001
>12 wk [26,66,86]	3	−14.25 (−19.03, −9.46)	<0.001	82%	0.004
Overall CPAP compared with controls					
Overall	25	−25.37 (−30.67, −20.07)	<0.001	96%	<0.001

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).

Mean baseline ESS score: normal/mild (0–9), moderate (10–15) and severe (16–24).

Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; I^2 proportion of total variability explained by heterogeneity.

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Table 5

Subgroup analysis of ESS results for comparison of MAD against conservative management (negative estimates favour MAD).

Subgroup	Number of studies	Difference in ESS: MAD-controls (95%CI)	P value for effect	I^2	Heterogeneity P value
Baseline AHI					
Mild [35]	1	−2.01 (−2.70, −1.32)	<0.001	42%	0.142
Moderate [24–26,33,48]	5	−1.38 (−2.48, −0.27)	0.15	73%	0.025
Severe [34,49,51]	3	−2.68 (−5.89, 0.54)	0.103	48%	0.051
Baseline ESS					
Moderate [24–26,35,49,51]	6	−1.36 (−2.07, −0.64)	<0.001	–	–
Severe [34]	1	−8.50 (−13.64, −3.36)	0.001	55%	0.037
Trial design					
Crossover [24,35,48,49]	4	−1.75 (−2.25, −1.25)	<0.001	2%	0.380
Parallel [25,26,33,34,51]	5	−2.18 (−4.80, 0.44)	0.102	68%	0.015
Duration of treatment					
2–12 wk [24,25,33,35,48,49,51]	7	−1.75 (−2.22, −1.28)	<0.001	0%	0.521
<12 wk [26,34]	2	−3.26 (−13.15, 6.63)	0.518	90%	0.001
Overall MAD compared with controls					
Overall	9	−1.64 (−2.46, −0.82)	<0.001	48%	0.051

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).

Mean baseline ESS score: normal/mild (0–9), moderate (10–15) and severe (16–24).

Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; DI: desaturation index; ESS: Epworth Sleepiness Scale; I^2 proportion of total variability explained by heterogeneity; MAD: mandibular advancement device.

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Table 6

Subgroup analysis of ESS results for comparison of MAD against CPAP (positive estimates favour CPAP).

Subgroup	Number of studies	Difference in ESS: MAD-CPAP (95%CI)	P value for effect	I^2	Heterogeneity P value
Baseline AHI					
Moderate [24–26,28,36,54]	6	0.06 (−0.61, 0.72)	0.864	0%	0.659
Severe [31,46,52,53]	4	1.42 (−0.24, 3.08)	0.094	68%	0.024
Baseline ESS					
Moderate [24–26,31,36,46,52–54]	9	0.81 (−0.04, 1.65)	0.062	49%	0.049
Trial design					
Crossover [24,28,36,46,53,54]	6	0.54 (−0.48, 1.57)	0.301	60%	0.030
Parallel [25,26,31,52]	4	0.97 (−0.16, 2.11)	0.093	0%	0.399
Duration of treatment					
2–12 wk [24,25,31,36,46,52–54]	8	0.82 (−0.09, 1.73)	0.078	55%	0.031
> 12 wk [26,28]	2	−0.06 (–1.66, 1.54)	0.944	0%	0.461
Overall MAD compared with CPAP					
Overall	10	0.67 (−0.11, 1.44)	0.093	45%	0.059

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).

Mean baseline ESS score: normal/mild (0–9) moderate (10–15) and severe (16–24).

Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; ESS: Epworth sleepiness scale; I^2: proportion of total variability explained by heterogeneity; MAD: mandibular advancement device.

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Table 7

Subgroup analysis of ESS results for comparison of CPAP against conservative management (negative estimates favour CPAP).

Subgroup	Number of studies	Difference in ESS: CPAP-control (95%CI)	P value for effect	I^2	Heterogeneity P value
Baseline AHI					
Mild [32,60,65,71,73]	5	−1.23 (−2.19, −0.27)	0.012	59%	0.045
Moderate [24–26,79,84–86,90,91,95]	10	−1.82 (–2.73, –0.92)	<0.001	60%	0.008
Severe [14,16,32,57–65,68,69,71–74,76–78,81,83,87,89,92,97]	22	−2.64 (–3.44, –1.84)	<0.001	86%	<0.001
Baseline ESS					
Normal/Mild [58,59,65,83,91	5	−0.83 (−1.16, −0.51)	<0.001	30%	0.222
Moderate [14,24–26,32,57,60–62,64,68,69,71–74,77,78,81,84–86,89,90,92,95,97,100]	28	−2.19 (−2.84, −1.53)	<0.001	76%	<0.001
Severe [16,63,76,79,87]	5	−4.99 (−6.51, −3.47)	<0.001	46%	0.115
Trial design					
Crossover [24,60,64,71–74,85,89,91,92,95];	12	−2.32 (−3.33, −1.31)	<0.001	79%	<0.001
Parallel [14,16,25,26,32,57–59,61–63,65,68,69,76–7981,83,84,86,87,90,97,100]	26	−2.15 (−2.74, −1.55)	<0.001	82%	<0.001
Duration of treatment					
2–4 wk [14,16,62,71–74,76,79,85,91,95,97]	13	−2.58 (−3.66, −1.51)	<0.001	75%	<0.001
5–12 wk [24,25,32,57,58,60,61,63,64,69,77,78,84,87,89,90,100]	17	−2.20 (−3.02, −1.39)	<0.001	68%	<0.001
>12 wk [26,59,65,68,81,83,86,92]	8	−1.87 (−2.83, −0.90)	<0.001	93%	<0.001
Overall CPAP compared with controls					
Overall	38	−2.23 (−2.76, −1.71)	<0.001	83%	<0.001

Mean baseline AHI (or DI if AHI not reported) events/hour: mild (AHI 5–14, DI 5–9), moderate (AHI 15–30, DI 10–30) and severe (AHI > 30, DI > 30).
Mean baseline ESS score: normal/mild (0–9), moderate (10–15) and severe (16–24).

Abbreviations: AHI: apnoea-hypopnoea index; CI: confidence interval; CPAP: continuous positive airway pressure; DI: desaturation index; ESS: Epworth sleepiness scale; I^2: proportion of total variability explained by heterogeneity; MAD: mandibular advancement device.