Obstructive sleep apnoea syndrome (OSAS) is a common sleep breathing disorder characterised by repetitive collapse or narrowing of the airway resulting in intermittent blood oxygen desaturations and fragmented sleep. OSAS, coupled with daytime sleepiness, affects at least 2–4% of the middle aged population. Sleepiness is a common presenting symptom of OSAS and may be measured by both subjective and objective methods. Other presenting symptoms include loud sonorous snoring, cognitive confusion, poor executive functioning, impaired quality of life, morning headaches, and hypertension. It is well established that continuous positive airway pressure (CPAP) effectively reduces obstructive sleep disordered breathing to levels regarded as normal. The most recent meta-analysis of randomised controlled trials has shown that the severe presentation of the syndrome (apnoea hypopnoea index (AHI) > 30/hour) is effectively treated with continuous positive airway pressure (CPAP). Until recently there have been insufficient data to determine whether CPAP improves sleepiness in the larger subgroup with mild to moderate OSAS (AHI 5–30/hour).

**Methods:** A systematic search of Medline and a hand search identified seven randomised controlled trials where CPAP was compared with either a placebo or with conservative management in the treatment of mild to moderate OSAS (AHI 5–30/hour). All trials used the Epworth Sleepiness Scale (ESS), four used the Multiple Sleep Latency Test (MSLT), and three used the Maintenance of Wakefulness Test (MWT) to measure sleepiness.

**Results:** Meta-analyses indicated that CPAP significantly reduced subjective daytime sleepiness (ESS) by 1.2 points (95% CI 0.5 to 1.9, p = 0.001), improved objective daytime wakefulness (MWT) by 2.1 minutes (95% CI 0.5 to 3.7, p = 0.011), but did not affect objective daytime sleepiness (MSLT, mean benefit −0.2 minutes, 95% CI −1.0 to 0.6, p = 0.6). The two significant effects were small (effect size < 0.30).

**Conclusions:** CPAP elicits small improvements in subjective sleepiness and objective wakefulness in people with mild to moderate OSAS. However, the effects on sleepiness are of limited clinical significance.

**Background:** Obstructive sleep apnoea syndrome (OSAS) affects an estimated 2–4% of the middle aged population. Meta-analyses of randomised controlled trials have shown that the severe presentation of the syndrome (apnoea hypopnoea index (AHI) > 30/hour) is effectively treated with continuous positive airway pressure (CPAP). Until recently there have been insufficient data to determine whether CPAP improves sleepiness in the larger subgroup with mild to moderate OSAS (AHI 5–30/hour).

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with OSAS were considered. One of the arms had to be either conservative management or placebo. Conservative management of OSAS usually includes advice about weight loss, sleep hygiene, adoption of non-supine sleep posture, and avoidance of alcohol and sedatives. Acceptable placebos included orally ingested placebo tablets or sham CPAP devices that did not improve overnight indices of sleep disordered breathing compared with baseline polysomnographic reports. Unacceptable comparisons included any device that improved sleep disordered breathing such as suboptimally pressured but partially therapeutic CPAP, or any surgical techniques including sham surgery or sham or ineffective mandibular advancement splints. Studies not exclusively analysing mild to moderate OSAS classification (AHI specified as 5–30/hour) were excluded. To be included, trials had to measure the Epworth Sleepiness Scale (ESS; a measure of trait subjective sleepiness, self-reported likelihood of dozing in common situations5), and/or the Multiple Sleep Latency Test (MSLT; a measure of state objective sleepiness, propensity to fall asleep6), and/or the Maintenance of Wakefulness Test (MWT, a measure of state objective wakefulness, the ability to resist sleep7). The ESS is a pencil and paper measure of the likelihood of falling asleep in eight everyday situations (each scored between 0 and 3) and is expressed as a score between 0 (not sleepy) and 24 (extremely sleepy). The two objective methods quantify daytime sleepiness by electrophysiologically measuring the average sleep latency across a number of nap opportunities in a single day. They mainly differ by the instruction to patients to “go to sleep” (MSLT) or to “stay awake” (MWT).

Data abstraction and trial quality assessment
Study and patient characteristics retrieved for each trial included: number of patients, placebo type, trial structure, length of follow up, sex balance, mean age, mean body mass index (BMI; kg/m²), mean AHI, method of measuring airflow (thermistor or pressure transducer), dropout rate, mean CPAP use per night, country of origin, and baseline severity of sleepiness measured by the ESS, MWT, and/or MSLT. The primary data analyses required the mean (SE) of the placebo sleepiness measured by the ESS, MWT, and/or MSLT. The primary data analyses required the mean (SE) of the placebo adjusted effects of CPAP on the ESS, MSLT, and/or MWT. The study effects on the pooled estimate (METAINF). Publication bias was evaluated visually using the funnel plot and statistically (META/BIAS) using Egger’s and Begg’s tests. Effect sizes24 were calculated by dividing the mean size of the effect by the baseline standard deviation of a suitable published comparison group of 110 untreated Australian patients with mild to moderate OSA.24

RESULTS
Systematic review
The systematic search of Medline identified 295 studies of further interest. An additional suitable study published outside the search dates was also included. The search terms used were not specific to our question. Thus, many of the studies identified were not randomised controlled trials, did not investigate OSAS, or involved paediatric patients or patients with OSAS and other serious co-morbidities. Many unsuitable trials investigated CPAP (or a similar such device) compared with mandibular advancement splints, autotitrating CPAP, bi-level PAP, or surgical procedures. A number of trials used what were described as “placebo CPAP machines”. On closer inspection these machines suboptimally reduced AHI and thus were not placebo devices. Another trial compared positional therapy with CPAP in a group of patients who had largely mild to moderate positional OSAS. Thus, the positional therapy might be expected to be beneficial to this subgroup and was not a valid placebo. After reviewing the abstracts of the remaining studies, 28 were randomised placebo/conservative management controlled trials of CPAP. Both reviewers independently...
agreed that seven of these investigated mild to moderate OSAS and were suitable for inclusion. Figure 1 shows the trial inclusion flow chart. All seven studies used the ESS,\textsuperscript{9–12, 14–16} four used the MSLT\textsuperscript{10–12, 14} and the remaining three used the MWT.\textsuperscript{9,15} The characteristics of the included trials are summarised in table 1, and table 2 summarises the patient characteristics from each of the trials. Five of the seven studies used nasal thermistors\textsuperscript{9–10, 12, 14, 15} to measure airflow while the remaining two used nasal pressure\textsuperscript{11,16} in accordance with recent guidelines.\textsuperscript{4} Trials using nasal thermistors might include more severely afflicted OSAS patients as this method is less sensitive to breathing disturbances than nasal pressure measurements.

Six studies scored 3 on the Jadad scale of trial quality. All these had adequate descriptions of trial dropouts and withdrawals in addition to being appropriately randomised. In one study it was unclear why dropouts had occurred.\textsuperscript{11} No studies were truly double blind as CPAP titrations require that at least some of the patients’ interactions with sleep staff require those staff being unblinded. This holds even where placebo CPAP devices are used.\textsuperscript{15}

Meta-analyses

After controlling for placebo effects, Epworth scores were significantly improved by CPAP by 1.2 points (95% CI 0.5 to 1.9, p = 0.001, fig 2). The random effects model was used because effects on the ESS were heterogeneous (Q = 13.1, df = 6, p = 0.04). Meta-regression indicated that heterogeneity was only related to one of the trial or patient characteristics extracted from the studies (tables 1 and 2 and also thermistor or pressure transducer measurement of SDB). Studies that had lower dropout rates had larger reductions in Epworth scores (Z = 2.38, p = 0.02). Mean compliance with CPAP therapy did not explain the heterogeneity in improvements on the ESS. CPAP still had a small but significantly greater than zero effect when crossover and parallel trials were analysed separately.

CPAP treatment led to an improvement in the MWT of 2.1 minutes (95% CI 0.5 to 3.7, p = 0.011) when using both fixed and random effects methods (fig 3). MWT effects were not heterogeneous (Q = 1.3, df = 2, p = 0.53). Only two of the studies measured MWT at baseline and were able to quantify the placebo effect. Barnes et al\textsuperscript{15} found a significant 2.7 minute worsening on placebo and Marshall et al\textsuperscript{14} found a non-significant 3.1 minute worsening while on placebo. These worsening sleep latencies contributed to the net effect of CPAP shown in fig 3.

The MSLT was used in four studies and worsened by a non-significant 0.2 minutes (95% CI –1.0 to 0.6, p = 0.74) with CPAP treatment after controlling for placebo effects using both fixed and random effects methods (fig 4). The effects on MSLT were not heterogeneous (Q = 1.2, df = 3, p = 0.74). A comparison analysis of MSLT and MWT latencies showed that the difference in sensitivities of –0.2 minutes and 2.1 minutes, respectively, was significant (Mann-Whitney U test, Z = 2.1, p = 0.03).

No single trial, when removed, significantly affected the overall estimate of effects. No evidence of bias was observed.

Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of patients</th>
<th>Control type</th>
<th>Crossover study</th>
<th>Treatment duration (weeks)</th>
<th>Dropout rate</th>
<th>MSLT or MWT</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engleman\textsuperscript{10}</td>
<td>16 and 9</td>
<td>Pill</td>
<td>Y</td>
<td>4</td>
<td>11%</td>
<td>MSLT</td>
<td>3</td>
</tr>
<tr>
<td>Redline\textsuperscript{9}</td>
<td>97</td>
<td>CT</td>
<td>N</td>
<td>10.5</td>
<td>13%</td>
<td>MSLT</td>
<td>3</td>
</tr>
<tr>
<td>Engleman\textsuperscript{9}</td>
<td>34</td>
<td>Pill</td>
<td>Y</td>
<td>4</td>
<td>8%</td>
<td>MWT</td>
<td>3</td>
</tr>
<tr>
<td>Monasterio\textsuperscript{15}</td>
<td>12</td>
<td>CT</td>
<td>N</td>
<td>24</td>
<td>12%</td>
<td>MSLT</td>
<td>2</td>
</tr>
<tr>
<td>Barnes\textsuperscript{1}</td>
<td>28</td>
<td>Pill</td>
<td>Y</td>
<td>8</td>
<td>33%</td>
<td>MWT</td>
<td>3</td>
</tr>
<tr>
<td>Barnes\textsuperscript{1}</td>
<td>80</td>
<td>Pill</td>
<td>N</td>
<td>12</td>
<td>30%</td>
<td>MWT</td>
<td>3</td>
</tr>
<tr>
<td>Marshall\textsuperscript{16}</td>
<td>29</td>
<td>Sham CPAP</td>
<td>Y</td>
<td>3</td>
<td>6%</td>
<td>MWT</td>
<td>3</td>
</tr>
</tbody>
</table>

CT, conservative treatment; CPAP, continuous positive airway pressure; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness Test.

Figure 2 Forest plot indicating that Epworth sleepiness scores were significantly improved by CPAP treatment. First author and year of publication of source trial are listed on the vertical axis. Horizontal lines represent 95% confidence intervals from each indicated study for the effects of CPAP after adjustment for control. Elongated diamonds indicate the mean (apex of diamond) and 95% confidence intervals for the pooled estimate of the effect. The size of the shaded boxes represents the weight given to that study. Larger boxes are studies that have given more precise estimates and they tend to be larger.

Table 2 Characteristics of patients in studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mean age (years)</th>
<th>Sex ratio (no of men)</th>
<th>Mean BMI (kg/m(^2))</th>
<th>Mean CPAP use (h/night)</th>
<th>Baseline ESS</th>
<th>Baseline MWT (min)</th>
<th>Baseline MSLT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engleman\textsuperscript{10}</td>
<td>52</td>
<td>75% (12)</td>
<td>30</td>
<td>2.8</td>
<td>14</td>
<td>10</td>
<td>NB</td>
</tr>
<tr>
<td>Redline\textsuperscript{9}</td>
<td>48</td>
<td>52% (50)</td>
<td>33</td>
<td>3.1</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Engleman\textsuperscript{9}</td>
<td>44</td>
<td>61% (21)</td>
<td>30</td>
<td>2.8</td>
<td>13</td>
<td>NB</td>
<td>10</td>
</tr>
<tr>
<td>Monasterio\textsuperscript{15}</td>
<td>54</td>
<td>86% (108)</td>
<td>29</td>
<td>4.8</td>
<td>12</td>
<td>10.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Barnes\textsuperscript{1}</td>
<td>45</td>
<td>83% (35)</td>
<td>30</td>
<td>3.5</td>
<td>11</td>
<td>30.7</td>
<td>20.9</td>
</tr>
<tr>
<td>Barnes\textsuperscript{1}</td>
<td>46</td>
<td>79% (63)</td>
<td>31</td>
<td>3.6</td>
<td>10.2</td>
<td>20.9</td>
<td></td>
</tr>
</tbody>
</table>

NB, no baseline measured; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness Test.
CPAP treatment of mild sleep apnoea

might be occurring in these patients.

indication that CPAP halts a decline in wakefulness that
due to the lack of placebo adjustment. This might also be an
effect that would be seen in clinical practice
meta-analysis might not therefore be an accurate indication
these crossover trials. The effect size estimated by the present
evidence of a slight test-retest worsening of MWT latencies in
difficult to maintain in these patients about the time they
real effect where wakefulness is becoming subtly more
by meta-analysis. This unexpected pattern might indicate a
effects noted worsening on the placebo arm which is similar
or larger in magnitude to the benefit of CPAP estimated here
by meta-analysis. This unexpected pattern might indicate a
real effect where wakefulness is becoming subtly more
difficult to maintain in these patients about the time they
are invited to participate in a clinical trial. It could also be
evidence of a slight test-retest worsening of MWT latencies in
these crossover trials. The effect size estimated by the present
meta-analysis might not therefore be an accurate indication
of the smaller effect that would be seen in clinical practice
due to the lack of placebo adjustment. This might also be an
indication that CPAP halts a decline in wakefulness that
might be occurring in these patients.

The observed heterogeneity of the ESS was associated with
the dropout rate, trials with low dropout rates showing
significantly larger improvements. However, this might be a
chance finding as it is in the opposite direction to that
normally expected. Improvements in ESS scores were not
related to mean compliance with CPAP or baseline disease
severity (ESS or AHI), a series of potentially important
mediators. Neither the MSLT nor the MWT was observed to
have significant heterogeneity. Sensitivity analyses of all
three outcome measures did not indicate any studies which
had undue influence upon the final estimated effects of
CPAP. Funnel plots and associated statistics offered no
evidence that the effects observed were due to selective
publication, but this was to be expected given the relatively
small size of these trials. While the tests for publication bias
do not show statistical significance, it is always possible that
a number of unpublished negative trials exist.

The combination of parallel and crossover trials into a
single meta-analysis is not regarded as statistically orthodox
because the estimates of standard error are not calculated in
the same manner. However, when these study designs were
separated, both analyses agreed that CPAP has a small but
significant effect on subjective sleepiness that is also highly
comparable to the analysis shown in fig 2. Neither type of
study indicated any change in MSLT latencies, and this is also
highly comparable to the effects summarised in fig 4. Despite
this agreement, our combination of these studies into single
meta-analyses remains a potential study weakness.

These results extend the recent meta-analysis by Patel and
colleagues3 by meta-analysing not only improvements in the
ESS score, but also MSLT and MWT improvements in
patients with mild to moderate OSAS. Patel et al found that
the mean benefit to subjective sleepiness in patients with
mild to moderate OSAS was a non-significant 1.1 points in
the ESS score compared with a significant 4.75 points for
patients with largely severe OSAS. The finding here that
subjective sleepiness improved by 1.2 points is almost
identical in magnitude, but was statistically significant due
to the additional power from the three most recent studies.

The applicability of the findings here is also strengthened by
the exclusion from the analyses of the study by Barbe and
colleagues13 which used CPAP to treat people with severe
sleep disordered breathing but no abnormal daytime sleepi-
ness. The study was not relevant for deciding whether to treat
a group of patients with mild to moderate sleep disordered
breathing and significant daytime sleepiness. In the studies
analysed by Patel et al MWT latency improved by a mean of
3 minutes. Our finding of a 2.1 minute improvement in MWT
latencies in a group of studies restricted to patients with mild
to moderate OSAS is in accordance with expectations, given
that the findings of Patel et al included patients with the full
spectrum of OSAS severity (including mild to moderate). It is
notable that the trials at the severe end of the disease
spectrum analysed by Patel et al were of similar duration and
design to the trials of mild to moderate OSAS analysed here.
The greater effects seen in trials of severe OSAS are therefore
due not to longer treatment durations. The paucity of effect is
also not due to the poor action of the treatment as it has long
been established that CPAP abolishes sleep disordered
breathing while the patient is wearing the device correctly.1
While Patel and colleagues did not find significant differences between MSLT and MWT treatment sensitivities, we have from the outset assumed that these metrics should not be combined as they measure different domains. MSLT and MWT latencies in other studies are not well correlated, are differentially sensitive to CPAP treatment, and probably measure different abilities. Separating the ability to fall asleep from the ability to sustain wakefulness also seems to be supported by findings from the literature indicating that these two phenomena arise from separate but interacting neurological processes. The 95% confidence intervals from the meta-analyses show that, while the MSLT scores are not significantly affected by CPAP treatment, the MWT scores are significantly improved (figs 2 and 3). Furthermore, these latencies are significantly different when combined in the same meta-analysis. We therefore conclude that MSLT and MWT latencies should not be combined, despite being measured in compatible units, because the two measurements are differentially sensitive to CPAP treatment and probably measure different aspects of increased sleepiness, at least in the specific patient group included here.

The improvements in sleepiness in this group are statistically significant, but it is not clear from the present analyses whether the benefit accrues equally to those across the mild to moderate spectrum or whether there exists a mean severity point at which CPAP therapy is more of a hindrance to good daytime function than the sleep disordered breathing it treats. It is also unclear whether the expense associated with ongoing CPAP treatment is cost effective in terms of the effects on daytime sleepiness. Cost effectiveness is an important consideration because the effect sizes are very small and close to being insignificant (<0.20). CPAP might have an expanded role in treating mild to moderate OSAS if it can be shown in randomised controlled trials to be a cost effective treatment for reducing the risk of cardiovascular disease.

In conclusion, CPAP significantly improves subjective sleepiness and objective wakefulness in patients with mild to moderate OSA; it does not improve objective sleepiness. However, the effect sizes of these adjustments are very small and may not be clinically relevant.

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This project was supported by the funding of a PhD stipend to NSM by Massey University and the Sleep Wake Research Centre.
Competing interests: none.

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