

Systematic review of the efficacy of nasal CPAP

Neil J Douglas

Continuous positive airway pressure (CPAP) therapy has been regarded for more than a decade by those in the field as the treatment of choice for the sleep apnoea/hypopnoea syndrome (SAHS). Nevertheless, two recent systematic reviews^{1,2} have appropriately pointed out that there is a shortage of robust evidence that CPAP benefits medium and long term outcomes in SAHS. However, the striking aspect of the two reviews is their diametrically opposed conclusions about the efficacy of CPAP, one concluding from the evidence that CPAP was indicated in patients with more than 20 apnoeas + hypopnoeas per hour of sleep plus daytime sleepiness,¹ whereas the other concluded that "the studies do not provide sufficiently robust evidence for the effectiveness of CPAP".² There are differences in the design of these reviews which may account for this disparity.

Systematic review should be impartial. The review by Wright and colleagues³ was funded, at least in the initial stages, by purchasing authorities concerned about the increasing costs of provision of sleep services and CPAP. Sackett has commented that there is a "fear that evidence based medicine may be hijacked by purchasers and managers to cut the costs of healthcare".⁴ The study by Wright *et al*³ would appear to be one such example. In contrast, the Australasian study¹ was commissioned by the Australian Medical Research Council and the New Zealand Ministry of Health.

Evidence based medicine has been defined as "integrating individual clinical expertise with the best available external clinical evidence from systematic research", where clinical expertise is "the proficiency and judgement that individual clinicians acquire through clinical experience and clinical practice".⁴ Wright and colleagues³ did not include in their panel any physicians with any experience of sleep apnoea; indeed, only one of the panel of five was medically qualified, a physician in public health medicine. In contrast, the Australasian review¹ had two physicians with experience in sleep medicine. Appropriately, these two were in a minority, the remainder of the panel comprising two physicians with broad experience of evidence based medicine and one anaesthetist. Furthermore, the recommendations of this panel were then revised by a panel of 10, none of whom were sleep physicians, to further guard against advocacy by the sleep clinicians.

Wright *et al*³ ignored the many acute studies showing that CPAP was effective in preventing obstructive apnoeas and improving sleep quality, whereas the Australasian study¹ included such investigations. The authors of the latter study also carried out a meta-analysis of medium term studies performed without placebo control and concluded that these pro-

vided evidence of a substantial impact of CPAP which was too great to be solely a result of bias.

The authors of both reviews agreed that at the time there was only one placebo controlled study examining the efficacy of CPAP,⁵ but came to radically different conclusions about its value. The Australasians¹ found "no major methodological threats to its validity" while Wright *et al*³ concluded that the "study had important weaknesses". Although these are not clearly specified, there appear to be three areas of concern: the placebo used, the lack of wash-out period, and the test used for differential carryover.

Engleman and colleagues⁵ used an oral placebo which was actively advocated to patients as an agent which might improve upper airway muscle function, this being done with approval of the local ethics advisory committee. This type of placebo was chosen after careful consideration of the alternative approaches, including the possible use of a CPAP mask attached to a CPAP machine delivering the lowest possible pressure, so-called "sham CPAP". Sham CPAP was rejected by Engleman *et al* for five reasons: (1) the wearing of a mask at night is likely to interfere with sleep, thus impairing daytime function and so falsely biasing in favour of active therapy; (2) CPAP at a subtherapeutic level had been reported at the time the study was designed to cause dangerous hypoxaemia; (3) sham CPAP would be readily identified by patients, thus unblinding a crossover study; (4) sham CPAP at a pressure sufficient to wash out carbon dioxide may prevent upper airway narrowing and thus be an effective therapy in some patients; and (5) it was not clear whether patients would comply with an obstructive placebo which could be detrimental to sleep and well being.

Wright *et al*³ also criticised the absence of a washout period between the two limbs in Engleman's study, but this could not be regarded as an "important weakness" of the study for two reasons. Firstly, any carryover effect of the active treatment would have biased against the positive findings of benefit with CPAP and, secondly, Engleman *et al* did not measure any of the outcomes until 28 days after crossover, whereas the effects of CPAP wear off within a day.⁷

Wright's criticism of the absence of tests of differential carryover are also not "important weaknesses" as any carryover would again have biased against the positive findings. Furthermore, carryover was sought by analysis of variance for all of the outcome measures and only found for the one variable reported, necessitating a different statistical approach for this variable.⁵

Respiratory Medicine
Unit, Department of
Medicine, University
of Edinburgh, Royal
Infirmary, Edinburgh
EH3 9YW, UK
N J Douglas

Correspondence to:
Professor N J Douglas.

Table 1 Mean (SD) treatment effects in 48 patients with AHI >15

	Baseline	Placebo	CPAP	p value
Sleepiness				
Mean sleep onset latency (min)	Not performed	6.2 (3.8)	7.9 (3.8)	<0.001
Epworth sleepiness score*	12 (4)	12 (4)	6 (3)	0.001
UMACL Energetic arousal	20 (6)	20 (5)	23 (5)	<0.001
Symptoms				
Symptom total†	5.0 (1.3)	4.0 (1.3)	2.3 (1.5)	<0.0001
Cognitive performance				
SteerClear (obstacles hit)†	100 (49)	73 (34)	67 (26)	0.03
TrailMaking B (s)†	79 (35)	70 (30)	67 (29)	NS
Digit symbol substitution	48 (11)	52 (12)	53 (12)	NS
Block design†	29 (9)	32 (9)	34 (8)	0.02
Performance IQ decrement	10 (11)	5 (11)	2 (11)	0.01
RVIP (correct)	29 (12)	37 (14)	36 (15)	NS
8-choice reaction time (ms)	356 (51)	343 (40)	345 (44)	NS
2 second PASAT	33 (9)	37 (10)	39 (11)	0.001
Verbal fluency (total)	38 (11)	41 (11)	40 (12)	NS
BVRT (correct)†	7.3 (2.1)	7.6 (1.4)	7.7 (1.6)	NS
Psychological well being				
HADS anxiety†	7.9 (4.1)	6.4 (4.4)	5.9 (3.7)	NS
HADS depression†	6.3 (4.1)	4.8 (4.0)	3.8 (3.3)	0.02
GHQ-28†	7.3 (6.7)	4.4 (5.5)	3.6 (5.1)	NS
NHP Pt 2†	9.3 (0.7)	7.2 (0.8)	5.6 (0.8)	NS

p values refer to comparison of placebo with CPAP.

*First assessments compared with Hills and Armitage.¹⁰

†Mann-Whitney test.

UMACL = UWIST mood adjective checklist; RVIP = Rapid visual information processing; PASAT = Paced auditory serial addition test; BVRT = Benton visual retention test; HADS = Hospital anxiety and depression scale; GHQ-28 = General health questionnaire-28; NHP = Nottingham health profile; NS = non-significant.

Thus, it seems the “important weaknesses” probably amount to concerns about the use of an oral placebo. The Australasian study expressed concern about the use of an oral placebo as well, but did not consider this invalidated the conclusions of the study. We acknowledge there is no perfect placebo for CPAP but feel that an oral placebo, as used in our study, is one of the better—or perhaps the best—options available and gives valid results.

Our major concern about the evidence of efficacy of CPAP is the dearth of corroborative data, a concern shared by the authors of both reviews.^{1 2} Since these reviews were conducted, one further placebo controlled study has been published by Engleman and colleagues⁸ which indicates improvements in symptoms, mood, and mental flexibility with CPAP, even in patients with only mild SAHS (5–15 apnoeas + hypopnoeas/hour). Having carried out searches using Medline and Embase, we were unable to identify any other controlled studies of CPAP in the literature. By contacting those involved in therapeutic research in SAHS we identified four further studies yet to be published. (1) The further report by Engleman *et al*⁸ of 23 patients with AHI of >15 who showed significant benefits from CPAP. When combined with the 25 patients in their original report who underwent an identical protocol,⁵ data on 48 patients with “severe” SAHS (AHI >15) show that CPAP improves symptoms, mood, subjective and objective sleepiness, and a range of cognitive functions (table 1). To place these findings in an appropriate context, the magnitude of the changes observed was as large as those reported for stimulant therapy in narcolepsy.¹¹ It must be stressed that this analysis also strongly illustrates the learning and placebo effects found in patients treated with CPAP, supporting the need for randomised controlled trials expressed in both previous reviews.^{1 2} (2) In a second study of

mild SAHS (defined as AHI of 5–15 plus subjective sleepiness), using a different range of tests but a similar oral placebo controlled design, Engleman *et al*¹² again found improvements in symptoms, subjective sleepiness, quality of life, and cognitive function. (3) Badia *et al*¹³ found significantly greater improvements in symptoms and quality of life with CPAP in comparison to conservative therapy which included a weight loss programme in a parallel group study. (4) Stradling *et al*¹⁴ reported significantly greater improvements in both subjective and objective sleepiness with active CPAP compared with sham CPAP in a parallel group study.

Thus, there are now five controlled studies all showing consistent improvements in symptoms and daytime function with CPAP in patients with SAHS. We were unable to identify any adequately powered and controlled studies yielding negative results. This consistency across five studies from three centres using three different control methodologies is strong evidence for efficacy of this therapy and is in keeping with the many uncontrolled reports received both from patients¹⁵ and physicians in the field. There is therefore a need for the benefits of CPAP therapy to be acknowledged by purchasers of health care so that sufferers from the syndrome can receive the benefits of optimal care.

- 1 Australian Health Technology Advisory Committee. The effectiveness and cost effectiveness of nasal continuous positive airway pressure in the treatment of obstructive sleep apnoea in adults. Canberra: Government Public Services, 1996.
- 2 Wright J, Johns R, Watt I, *et al*. Health effects of obstructive sleep apnoea and effectiveness of continuous positive airway pressure: a systematic review of the research evidence. *BMJ* 1997;314:851–60.
- 3 Wright J, Dye R. Systematic review of obstructive sleep apnoea; its effect on health and benefit of treatment. Nuffield Institute for Health, 1995.
- 4 Sackett DL, Rosenberg WM, Gray J, *et al*. Evidence based medicine; what it is and what it is not. *BMJ* 1996;312:71–2.
- 5 Engleman HM, Martin SE, Deary IJ, *et al*. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 1994;343:572–5.
- 6 Kreiger J, Weitzenblum E, Monassier JP, *et al*. Dangerous hypoxaemia during continuous positive airway pressure treatment of obstructive sleep apnoea. *Lancet* 1983;ii:1429–30.
- 7 Kribbs NB, Pack AI, Kline LR, *et al*. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147:1162–8.
- 8 Engleman HM, Martin SE, Deary IJ, *et al*. Effects of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax* 1997;52:114–9.
- 9 Engleman HM, Martin SE, Kingshott RN, *et al*. Randomised, placebo-controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 1998;53:341–5.
- 10 Hills M, Armitage P. The two period crossover trial. *Br J Clin Pharmacol* 1979;8:7–20.
- 11 US Modafinil in Narcolepsy Multicenter Study Group. Modafinil for the treatment of pathological somnolence in narcolepsy. *Neurology* 1998 (in press).
- 12 Engleman HM, Deary IJ, Douglas NJ. Daytime function after CPAP and placebo in patients with mild sleep apnoea/hypopnoea syndrome. *Am J Respir Crit Care Med* 1997;155:A846.
- 13 Badia JR, Hernandez L, Lyon C, *et al*. Efficacy of CPAP treatment in moderate to severe sleep apnoea/hypopnoea syndrome. *Eur Respir J* 1997;10(Suppl 25):310S.
- 14 Stradling JR, Jenkinson C, Davies RJ, *et al*. Randomised, sham-placebo controlled, parallel study of nasal continuous positive airway pressure for the treatment of obstructive sleep apnoea: interim analysis. *Am J Respir Crit Care Med* 1998 (abstract in press).
- 15 Engleman HM, Jirhandeh-Asgari N, McLeod AL, *et al*. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest* 1996;109:1470–6.