RESPIRONICS

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20/07/07

Re: Respironics UK submission for the health technology appraisal of continuous positive airways pressure (CPAP) for the treatment of obstructive sleep apnoea/hypopnoea syndrome (OSAHS).

Dear Mr Feinmann

Thank you for sending the assessment report produced by the NHS Centre for Review & Dissemination and Centre for Health economics – York Assessment Group for the above appraisal to Respironics.

My colleagues and I at Respironics felt that this was an extremely well researched and written appraisal report that clearly highlights the benefits of CPAP technology. In particular I am grateful to Steven Coughlin PhD, Senior Clinical Research Associate at Respironics International for help in composing this response.

Advanced technologies such as humidifiers, automatic positive airways pressure (APAP), pressure relief during exhalation (PR-CPAP) and bi-level therapy have so far not been considered in the assessment report. Several studies have investigated the efficacy of these advanced technologies, their effects on compliance and clinical outcomes, and their economic benefits against CPAP in OSAHS. Evidence for these technologies is outlined below. We believe they warrant consideration in the technology report and welcome the comments of the authors.

The section highlighted in yellow contains confidential information. A reference list follows the main body of the letter.

<u>Humidification</u>

A number of studies have demonstrated that heated humidification of CPAP reduces upper airway symptoms and increases initial compliance. A small study of six normal volunteers found that heated humidification produced an approximately 50% improvement in nasal resistance, while a cold, passover humidifier had no significant effect (1). In support of this, de Araujo and colleagues in a study of 25 patients with OSAHS receiving long-term nasal CPAP therapy and complaining of nasal discomfort, demonstrated that inhaled air dryness during CPAP therapy can be significantly attenuated by heated humidification, even during mouth leaks (2).

In a randomised, crossover study published in 2003, 42 subjects with OSAS were randomised to 3 weeks CPAP treatment with heated humidification or placebo humidification (3). Objective and subjective CPAP use, upper airway symptoms, and treatment satisfaction were compared. CPAP treatment with heated humidification reduced the frequency of adverse upper airway symptoms and overall CPAP use was greater over the 3 week follow-up period, but not subjective sleepiness or treatment satisfaction.

In 1999 Massie and co-workers evaluated the effects of humidification on nasal symptoms and compliance in 38 OSAHS patients using CPAP (4). 3 weeks of heated humidity and cold passover humidity were applied to each patient in a random order separated by a 2 week washout period with no therapy. CPAP use was significantly higher with heated humidity (5.52±2.1 h/night) when compared to CPAP without humidity (4.93±2.2 h/night; $p = 0.008$). Compliance differences were not observed when comparing CPAP use with cold passover humidity and CPAP use without humidity. Patients were more satisfied with CPAP when used with heated or cold passover humidity ($p<0.05$), however, only heated humidity resulted in feeling more refreshed on awakening ($p<0.05$). Dry mouth, throat and nose were reported less frequently when CPAP was used with heated humidity ($p<0.001$). In addition, Marshall and colleagues showed that humidification improves subjective and possibly also objective wakefulness (5).

In contrast two studies have reported that heated humidification offers no additional benefit in improving compliance, the subjective response to CPAP or quality of life, but may be associated with fewer symptoms attributable to the upper airway (6;7).

APAP

A wealth of studies have been published comparing efficacy, device preference, compliance, clinical outcomes, and the economic benefits of APAP against CPAP in OSAHS. Findings have not always been consistent between these studies possibly because of differences in the APAP algorithms employed by different manufacturers and device characteristics such as handling, size, weight and noise level, however, we feel that there is enough positive evidence to suggest an advanced role for this technology in the treatment of OSAHS.

Additionally, a search of the ICRCTN *meta*Register uncovered a large multicentre study currently being conducted in Switzerland, comparing the long-term Effectiveness of APAP against CPAP in OSAHS (ClinicalTrials.gov identifier - NCT00280800) highlighting the worldwide interest this technology is generating amongst the medical and scientific community.

Efficacy

The majority of physicians would now agree that APAP is as effective at controlling the respiratory disturbances associated with OSAHS as CPAP at lower mean pressures. Konermann and co-workers compared the ability of APAP and CPAP to suppress respiratory disturbances and improve sleep quality in 50 patients with confirmed severe OSAHS (8). At polysomnographic follow-up the respiratory disturbance index dropped by 93.6% (from 35.5±9.6/h to 2.4±1.6/h) in APAP and 91.5% (from 38.3±13.9/h to 3.6±4.4/h) on CPAP. Sleep efficiency on therapy was similar between the groups and normal sleep structure was largely restored.

In support of this Nussbaumer et al., in a randomised, double-blind, controlled, cross-over trial the comparing efficacy of APAP and CPAP delivered by the same device in 30 OSAHS patients, demonstrated that the apnoea hypopnoea index was similarly improved on each device (6.6 ±0.6 and 4.6±0.7/h, all $p<0.05$ vs. baseline) (9). Nolan and co-workers in a study of 29 patients with mild to moderate OSAHS showed no differences in polysomnographic variables between APAP and CPAP (10). Senn and colleagues in a study of 29 patients with severe OSAHS treated over three consecutive 1-month periods with two different APAP devices and a CPAP device in a random order demonstrated significant but comparable improvements in the apnoea hypopnoea index from baseline between APAP and CPAP (11).

Continuous adaptation of mask pressure to the needs of the patient could result in a decrease in pressure and therefore increase comfort. A number of studies have demonstrated that mean applied mask pressure during long-term APAP therapy is generally lower than manually titrated pressure under CPAP. In the study by Senn and colleagues, mean mask pressures on both APAP devices were significantly lower than on CPAP (11). A study from Essen, Germany, published in 2000 supports this (12). In this study 10 patients with sever OSAHS were randomly allocated to 2 months APAP or CPAP at the manually titrated pressure. Machine-scored AHI, P50, and median leak were recorded on 12 nights in each arm, and averaged. Mean P50 was 23% lower on APAP (7.2±0.4 cmH2O vs. 9.4±0.6 cmH2O, p<0.0001. Auto "recommended" pressure was also significantly lower on APAP 10.1±0.5 cmH2O, p=0.04 vs. CPAP) and median leak significantly lower (0.181±0.006 $L.s^{-1}$ vs. 0.20±0.006, p=0.003.

Data from several other studies support this conclusion. Konermann and co-workers demonstrated that mean mask pressure was 6.5±1.7 cmH2O on APAP and 8.1±2.5 cmH2O on CPAP (p<0.01) (8). Nolan et al. showed that mean pressure levels were significantly lower on APAP than CPAP (6.3±1.4 vs. 8.1±1.7 cm H_2O, p<0.001) (10). In a randomised crossover study by Massie et al. comparing 6 weeks of APAP and CPAP therapy, median and 95th centile pressures were lower when using APAP (p=0.002) (13).

Device Preference

Given its equal efficacy and lower applied mean pressure one would expect that patients would prefer APAP over CPAP. Three main studies have surveyed device preference amongst patients who have used both APAP and CPAP. In 2006 Nussbaumer et al. demonstrated that approximately 87% of patients studied preferred APAP to CPAP (p<0.001) (9). Nolan and colleagues advanced this finding, showing that approximately 67% of the patients requiring higher fixed pressures (≥8cmH2O) preferred APAP, whereas approximately 88% of the patients requiring lower pressure (<8cmH2O) preferred CPAP (p=0.03) (10).

In contrast when asked whether they preferred APAP to CPAP, 72% of the patients in the study by Senn and colleagues had no preference, and approximately 14% favoured APAP and 14% favoured CPAP (11).

Compliance

Improving compliance to further reduce the associated complication of OSAHS is one of the most important aspects of CPAP therapy. Compliance with APAP has been shown in some studies to be higher than with CPAP but this finding has not been consistent. In the study by Konermann and co-workers compliance, defined as the number of nights per week of mask appliance, was significantly better on APAP (6.5±0.4 vs. 5.7±0.7 to; p<0.01) (8). In 2003, Massie et al. advanced this finding (13). In this study 44 patients with OSAHS requiring high CPAP pressures were assigned to 6 weeks of laboratory determined CPAP and 6 weeks of APAP in a random order. Average nightly use was significantly higher when using APAP (306 minutes vs. 271, p=0.005).

In contrast, the study by Senn and colleagues showed no difference in the mean hours of device use per night between APAP and CPAP over 1 month, or the percentage of nights during the treatment period that patients used their machines for greater than 2.5 hours (11). The study from Essen, Germany, published in 2000 supports this. In this study, compliance was demonstrated to be 6.3±0.4 h on APAP and 6.1±0.5/h on CPAP (12). Likewise, in the study by Nussbaumer et al. patient compliance was similar on both APAP and CPAP (9).

Clinical Outcomes

Despite suggestions that compliance may be higher on APAP it is still not clear whether this therapy provides any further improvements in subjective and objective sleepiness and quality of life over CPAP. In the study by Massie et al. APAP resulted in improved SF-36 Vitality and mental health scores (65±20 vs. 58±23, $p<0.05$; 80±14 vs. 75±18, $p<0.05$) compared to CPAP, but no significant differences in subjective sleepiness ($p=0.065$) (13).

In contrast, after 1 month of each treatment, the study by Nussbaumer et al. demonstrated that subjective sleepiness and quality of life were similarly improved on both devices (9). Similarly the study by Nolan and co-workers showed no difference in subjective sleepiness between devices (10).

Economic Benefits

Since APAP does not require an initial titration, there may be cost saving for this device over CPAP. Planes et al. compared the cost of APAP initiated at home versus CPAP initiated in the sleep laboratory in 35 patients with severe OSAHS randomly assigned to the treatment arms (14). Over the treatment period both treatments produced similar valid improvements in clinical outcomes. The time from diagnosis to final adjustment of their therapy device was shorter with APAP than CPAP (16.3±5.0 vs. 47.2±46.5). Over the two month initial diagnosis and treatment period the cost of therapy per patient using APAP was significantly lower (1263±352 vs. 1720±455 Euros, $P<0.05$) than CPAP.

APAP Algorithms

Two recent studies have suggested that differences between the APAP algorithms of device manufacturers may influence their effect technical performance and clinical efficacy. Nolan and colleagues compared three different APAP devices for four weeks each (Autoset Spirit, Breas PV10i and the RemStar Auto) in a randomised crossover trial of 27 patients middle-aged (25 males) who were previously diagnosed with severe OSAHS and had been established on CPAP therapy for greater than 3 years (15). Mean pressure and patient compliance were significantly lower on the Breas PV 10i than the other APAP devices which were similar in this respect. Patients reported that the RemStar Auto was the quietest machine and the Autoset Spirit the noisiest and also the least preferable in terms of size. The Breas PV10i provided significantly poorer sleep quality in comparison to the other two APAP devices and more pressure discomfort.

In a study by Prof. Pevernagie's group from Ghent in Belgium, the titration performance of two devices based on detection of inspiratory flow limitation, the Respironics REMstar Auto and the ResMed Spirit, were compared (16). Fifty obstructive sleep apnoea patients were studies overnight using split-night polysomnography in a double-blind randomised crossover design. No significant differences were found in sleep parameters, subjective sleep quality and snoring index, however, the REMstar Auto was associated with a significantly lower apnoea-hypopnoea index in comparison with the ResMed Spirit (6.9±11.6/h vs. 9.4±9.2/h, $p = 0.004$), at significantly lower pressure levels (P95 9.2±2.3cm H_2O vs. 10.2±1.5cmH_2O, $p = 0.001$).

PR-CPAP

When PR-CPAP was first introduced to the market some clinicians voiced concerns that decreasing pressure at the beginning of exhalation could cause airway instability leading to breakthrough respiratory events. Two studies have addressed this point. Firstly, Dr Loube from Seattle demonstrated in a split night in laboratory polysomnographic comparison of C-Flex

(Respironics PR-CPAP) and CPAP in 16 patients with mild to moderate OSA that AHI and sleep efficiency were not significantly different (17). Likewise, Jerrentrup and co-workers in a study of eight subjects with treated OSA studied polysomnographically including measurement of inspiratory flow and oesophageal pressure demonstrated that there is no increase in the number of flow limited breaths between C-Flex at all settings compared to CPAP (18).

Additional evidence from Allentown, US, suggests that C-Flex might even provide a more effective therapy than CPAP (19). In this study subjects underwent one night of polysomnography in a single-blind, non randomised split night format receiving C-Flex at all three settings and CPAP. These data showed that C-Flex gave a similar or lower AHI, although these were not significant, and significantly greater sleep efficiency than CPAP. Likewise the arousal index was significantly improved for C-Flex levels 1 and 3.

Compliance has also been demonstrated to be higher on PR-CPAP. In a randomised, controlled trial of C-Flex versus CPAP Aloia and colleagues demonstrated that at the two to four week follow-up the average use per night was 0.7 hours longer for patients using C-Flex and that this margin increased to 1.7 hours at nine to 12 weeks (20). However, despite demonstrating increased compliance in the C-Flex group, clinical outcomes were not different. Data from a multicentre randomised controlled trial of CPAP versus C-Flex presented at the ATS annual conference in 2005 supports this (21). In this study of 142 newly diagnosed OSA patients C-Flex resulted in higher compliance (mean C-Flex 5.88±1.5 hrs. vs. CPAP 5.28±1.6 hrs, $p < 0.05$) and improved alertness at 90 days of treatment. In contrast, a study from Hagen, Germany showed no difference in compliance after seven weeks of therapy between patients using C-Flex and standard CPAP but reported that patients using C-Flex experienced less dryness of the mouth during the first night of therapy (22).

Bi-level therapy

Whilst bi-level therapy has been shown to be as effective as CPAP for the treatment of OSAS but offers no advantages in patients receiving first-time therapy for OSAS, there is some evidence that bi-level therapy is an effective rescue therapy in patients who are resistant to, or cannot tolerate CPAP therapy.

In 1998 Resta and colleagues demonstrated that there is a subset of OSAHS patients in whom bi-level therapy may be a better treatment modality (23). 286 consecutive OSAHS patients were studied. After a full night diagnostic polysomnography patients had a second full night under CPAP. If CPAP was not tolerated, or failed to correct breathing abnormalities during sleep, a second PSG, was performed, using a bi-level device. CPAP was considered a satisfactory therapy in 77% of patients. 23% required bi-level therapy. The majority of these patients had either obesity hypoventilation syndrome or chronic obstructive pulmonary disease.

Auto Bi-level Therapy

Whilst it is clear that bi-level therapy offers a therapeutic alternative for a subgroup of OSAHS patients, the burden of performing manual titrations in the sleep laboratory is often difficult due to the high technological and economic burden. In 2006 Respironics introduced the first auto-adjusting bi-level sleep system designed to reduce this burden.

At the 2006 APSS conference Dr Wylie's group presented a study investigating the clinical efficacy of BiPAP Auto compared to manually titrated BiPAP (24). Seventeen patients with confirmed OSAHS who were free of other sleep disorders underwent three sleep studies. On the first night conventional bi-level pressures were determined. On the second and third night

therapy was randomised. On one of these nights conventional bi-level therapy was applied using the pressures determined on night 1 and on the other patients received BiPAP Auto therapy set to deliver between 4 and 20cmH_20. There were no significant differences in sleep architecture. Both devices significantly reduced the AHI despite the BiPAP Auto delivering a significantly lower average IPAP. All other measures of IPAP and EPAP were similar between devices. These data suggest that the BIPAP Auto treats OSA as effectively as manually titrated BiPAP therapy.

An interim analysis of a study to be presented at the ERS in Stockholm in September investigated the efficacy of BiPAP Auto when applied as a rescue therapy in 11 optimally treated OSAHS patients with low APAP compliance of no other modifiable cause. Compliance significantly increased from 1.5+/-0,8 hours per night at baseline to 4.7+/-2.1 ($p<0,001$) at 2 weeks and this increase was maintained at 12 weeks. A further interim analysis containing 26 patients maintained these conclusions (Data in file).

In summary, Respironics feels that the high number of published studies investigating the effects of advanced technologies that we have highlighted in this letter warrant consideration as part of this technology report and hope that NICE will consider appraising these in future drafts.

Thank you for taking the time to consult with Respironics on this matter.

Yours Sincerely

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