Nasal Expiratory Positive Airway Pressure (Provent)
National PBM Monograph

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Introduction

The gold standard for treating obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP). Other modes of delivery are also available such as bilevel (BPAP) and autotitrating modes (APAP).

Nasal expiratory positive airway pressure (EPAP) is a new treatment option for patients with OSA. Provent is the only FDA approved product at this time. Other non-CPAP interventions for OSA include behavioral measures (e.g., weight loss, positional therapy, avoidance of alcohol and sedatives before bedtime, etc), oral appliances, and surgery in appropriate patients.

The diagnosis of OSA is confirmed during polysomnography (PSG) if the number of obstructive events is or greater than 5/hour in patients who have symptoms associated with OSA (e.g., witnessed apneas, snoring, gasping/choking at night, unexplained excessive sleepiness, non-refreshing sleep, etc.) or greater than 15/hour regardless of associated symptoms. The apnea-hypoxia index (AHI) is the average number of disordered breathing events per hour. An AHI $\geq$ 5 and < 15 is considered mild, $\geq$ 15 and $\leq$ 30 as moderate, and >30/hour as severe OSA.

Device

Provent consists of a 1-way valve that is inserted into each nostril and held in place by a hypoallergenic adhesive. Inspiratory resistance of the valve is minimal whereas expiratory resistance is 80cm H2O/L/sec at a flow rate of 100mL/sec. Resistance created during exhalation by the nose maintains a constant pressure in the posterior pharyngeal region and keeps the airway open until the start of the next inhalation.

Possible mechanisms of action are 1) increased functional residual capacity, producing tracheal traction and reducing upper airway collapsibility and 2) passive dilatation of the airway by the expiratory pressure, carrying over into inspiration 3) mild hypercapnea that occurs from hypoventilation induced by expiratory resistance of EPAP resulting in increased respiratory drive.[9]

FDA Approved Indication(s)

Treatment of OSA

Administration

Each pouch contains 2 valves, 1for each nostril, and is intended for single use. The product information sheet provides instructions on proper application. The device works by creating resistance during exhalation through the nose thereby creating the pressure needed to treat OSA. It may take up to a week or longer before the patient feels comfortable breathing while wearing the device. While trying to fall asleep, it is suggested that the patient inhale through their mouth or the device and exhale through their mouth. Once asleep, people generally switch to nasal breathing which is needed in order for the device to work.

Provent is also available as a starter kit specifically designed to help patients acclimate to therapy by gradually increasing the resistance when exhaling through the nose (expiratory resistance). The 30-day starter kit is divided in to 3 phases:

- Phase 1(low resistance) for nights 1-2
- Phase 2 (medium resistance) for nights 3-4
- Phase 3 (normal resistance) nights 5-30

Efficacy

There are 4 clinical trials that evaluated Provent beyond single night use; one was randomized, double-blind, sham-controlled. In the other trials all patients received the device and results were compared to control (off device).[1-4] The longest trial was 3 months in duration with a 12-month extension in a subgroup of patients.[1, 2]

Patients underwent sleep studies (polysomnography) to evaluate effectiveness of the product. Polysomnography was performed using standard techniques and events scored as described in the American Academy of Sleep Medicine Scoring Manual.

The primary endpoint was change in the AHI. Other endpoints included the change in AHI during REM and NREM sleep, change in AHI supine and non-supine, apnea index, oxygen desaturation index, oxygen saturation, impact on sleep efficiency and sleep architecture, and daytime sleepiness. See **Table 1** for definitions of the endpoints.

The studies by Berry and Kryger evaluated EPAP with an expiratory flow resistance of 80cmH2O/L at flow rate of 100ml/s (marketed product). The studies by Walsh and Rosenthal tested resistances of 50, 80, or 110cmH2O/L. In the later 2 trials, the results were combined for the various resistances tested.

Table 1: Definitions of Endpoints Evaluated in Clinical Trials

Apnea	Cessation of airflow for at least 10 seconds
Hypopnea	Reduction in airflow with resultant desaturation of ≥ 4%
Apnea-hypopnea index (AHI)	Averaged frequency of apnea and hypopnea events per hour of sleep An AHI ≥ 5 and < 15 is considered mild, ≥ 15 and ≤ 30 as moderate, and >30/hour as severe OSA.
Apnea index	Average number of apnea events per hour
Oxygen desaturation index (ODI)	Number of times that the oxygen saturation falls by more than 3 or 4 percent per hour of sleep
Arousal index	Arousal is an abrupt change from sleep to wakefulness or from a deeper stage of NREM sleep to a lighter stage. The arousal index is total number of arousals and awakenings per hour of sleep
Sleep architecture	Cyclical pattern of sleep as it shifts between the different sleep stages including NREM and REM sleep
Sleep efficiency	Ratio of time spent asleep (total sleep time) to the amount of time spent in bed
Epworth Sleepiness Scale (ESS)	Epworth Sleepiness Scale - index of sleep propensity during the day as perceived by patients, and derived from the answers to 8 questions

Apnea-Hypopnea Index

The AHI significantly improved with EPAP compared to the patient's value at baseline or while the device was not worn; however, mean AHI was still abnormal in patients with moderate-severe OSA. **Tables 2 and 3** show average AHI in the overall population and broken down according to OSA severity. In the RCT by Berry et al., 50.7% of patients had AHI reduction ≥50% or AHI reduced to <10/h compared to 22.4% in the sham group.[1]

The AHI was reduced during both NREM and REM sleep and while in the supine and non-supine positions. However, in the study by Berry et al., the difference between EPAP and sham were not significant for AHI NREM and AHI non-supine[1] (See **Appendix 1**).

Table 2: Clinical Trial AHI Results

Study	Design	n	Treatment arms	Duration	AHI (device-off)	AHI (device-on)
Berry (2011)	Randomized, double-blind, Parallel, sham-controlled	250	EPAP (n=127) Sham (n=123)	3 months	14.4 (5.5, 21.4) 10.2 (3.4, 19.3)	5.6 (2.1, 12.5) †* 8.3 (4.2, 20.6)
Kryger 2011	Extension trial of Berry et al. Open-label, no control arm	41	EPAP	12 months	15.7	4.7*
Walsh (2011)	Open-label, no control arm	59	EPAP	5-weeks	43.3±29	27.0±26.6*
Rosenthal (2009)	Open-label, no control arm	34	EPAP	30 days	24.5±23.6	15.5±18.9*

Values shown as median (25, 75 quartiles or mean±SD
†Significant vs. sham
*Significant on-device vs. off-device

Table 3: AHI, Apnea Index, and ODI According to OSA Severity

	Mild OSA (n=67)		Moderate OSA (n=68)		Severe OSA (n=56)	
	Control night	Treatment night	Control night	Treatment night	Control night	Treatment night
Apnea-hypopnea Index	9.6±3.2	6.5±7.2	20.7±4.6	10.0±8.1	57±23.5	33.0±28.0
Apnea index	4.9±3.6	3.1±4.4	13.3±6.7	5.9±7.5	41.0±24.5	19.0±22.9
Oxygen desaturation index	7.1±5.1	5.8±7.8	16.4±12.1	10.3±9.2	44.5±25.2	28.5±25.6

Information obtained from product information sheet

Oxygenation

The oxygen desaturation index (ODI) was significantly reduced with EPAP versus control/device-off in 3 studies.[1,2,4] In the fourth study by Rosenthal, the difference was not significant (See **Appendix**).[3] There was also a significant decrease when broken down by OSA; however, the index remained high for those with more advanced OSA **(Table 3)**.

Sleep Efficiency/Architecture

Average total sleep time was reduced by approximately 16 minutes with EPAP versus control/device-off (value was significant only in the study by Berry). Trials that evaluated sleep efficiency found no significant difference between EPAP and off-device. [3, 4] Three studies evaluated arousal index; 2 found a significant reduction [2, 4] and the third did not[1] (See **Appendix**). There were no clinically significant changes in the sleep stage durations.

Evaluation of sleepiness

Epworth Sleepiness Scale (ESS) is a validated tool, for OSA, used to subjectively measure a patient's sleepiness. Using a scale ranging from 0 to 3 (no chance of dozing to high chance of dozing) the patient rates their chance of dozing during 8 activities. The total ESS score can range from zero to 24, with higher scores correlating with increasing degrees of sleepiness: 1-6 points (normal sleep); 7-8 points (average sleepiness); 9-24 points (abnormal possibly pathologic sleepiness).

The mean ESS scores were relatively low at baseline. Significant improvement was seen in ESS scores using EPAP. Note that in the RCT, the score on sham also significantly improved; however, the improvement seen with EPAP was significantly greater compared to sham[1]. In a subset of patients with higher baseline ESS scores (mean 14), the mean ESS score dropped into the normal range. [1, 4]

Table 4: Epworth Sleepiness Scale

Study	n	Treatment arms	Duration	Baseline ESS score	ESS score on EPAP/sham
Berry (2011)	250	EPAP (n=127) Sham (n=123)	3 months	9.9±4.7 9.6±4.9	7.2±4.2*† 8.3±5.1*
Kryger 2011	41	EPAP	12 months	11	6*
Walsh (2011)	59	EPAP	5-weeks	12.5±5.1	8.7±4.4*
Rosenthal (2009)	34	EPAP	30 days	8.7±4.0	6.9±4.4*

†Significant vs. sham

*Significant on-device vs. off-device

Retrospective Analyses

Retrospective data of patients using Provent in the clinical practice setting have been presented as abstracts.[5-7] In 2 trials, the patient population included those who were current CPAP users or had failed or were intolerant to CPAP. [5, 7] Patients were provided with 5-10 nights of Provent for in-home acclimation. Patients that acclimated were asked to return for efficacy confirmation via PSG. Mean AHI was significantly reduced regardless of the severity of OSA. See **Appendix 2** for details.

Adherence to therapy

Adherence to Provent therapy was monitored by patient-completed diaries. Self-reported adherence was >88%; however, caution should be exercised when interpreting self-reported data.

Table 5: Adherence to Therapy

Study	Treatment arms	Duration	Adherence to Therapy
Berry (2011)	EPAP (n=127) Sham (n=123)	3 months	Median % (25, 75 quartiles) of nights device was worn for entire night EPAP: 88.2% (67.5, 96.4) Sham: 93.2% (84.0, 97.5)
Kryger 2011	EPAP	12 months	Median % (25, 75 quartiles) of nights device was worn for entire night EPAP: 89.3% (81.8, 95.2))
Walsh (2011)	EPAP	5 weeks for those meeting efficacy criteria	All patients with 1 week use (n=43): EPAP was used 94.2% nights for 91% of the nights Patients meeting efficacy criteria (n=21): EPAP was used 95.5% nights for 93% of the nights
Rosenthal (2009)	EPAP	30 days	% nights device was worn: 94.4%

Fifty-one patients were eligible to enter the 12-month extension trial by Kryger et al, however, 5 chose not to participate because they did not want to continue EPAP and 3 preferred to seek other therapy.[2]

Predictors of Response

Three studies attempted to determine if there are specific patient characteristics that predict response to Provent.[4, 7-8] In the retrospective analysis by Hwang et al., the profile of responders/non-responders did not reveal differences in demographic or baseline values other than all women with post-test PSG (n=14) were responders (defined as AHI↓50% and ≤ 15) to Provent.[7]

In Walsh et al., there was no difference in age, sex, BMI, weight, baseline ESS between those meeting and not meeting efficacy criteria (>50↓ AHI or <10 or >30%↓ with ESS ↓ ≥2) at the second PSG. More patients (14/18) who had Mallampati scores <4 met the efficacy criteria compared to 40% of those with a score of 4. In anesthesiology, the Mallampati score, also Mallampati classification is used to predict the ease of intubation. A high Mallampati score (class 4) is associated with more difficult intubation as well as a higher incidence of sleep apnea. They also noted that the non-efficacious group had higher AHI and lower SaO2 at baseline compared to the efficacious group; however, the authors point out that 25% of those with AHI >40 met the efficacy criteria.[4]

Another study that looked at single night use in 19 patients found a trend that those with positional or milder sleep disordered breathing in the lateral position were more likely to respond.[8]

Adverse Events/Safety

The most commonly reported adverse events were nasal congestion, nasal discomfort, insomnia, headache, dry mouth, dry throat, and discomfort with the device. There were no serious device-related adverse events reported in the clinical trials.

In Berry et al., 53/119 (44.5%) of patients receiving EPAP reported a device-related AE versus 37/110 (33.6%) in the sham group.[1] The number of device-related events was 106 and 63 for EPAP and sham respectively. Eight patients dropped out of the study because of AEs compared to 1 patient in the sham group. The reasons were dry mouth/throat (3), breathing discomfort (2), nasal itching (1), sleep maintenance insomnia (1), and vertigo (1).

In Walsh et al, 12/59 patients did not tolerate the device during the initial 1 week period of study and did not continue the trial. [4] The most commonly reported reasons were difficulty breathing and difficulty sleeping.

In 2 of the retrospective studies, 75% and 80% of patients were able to acclimate to a 10-day in-home trial of Provent and returned to clinic for PSG testing. [5,6] In a third trial, 49% returned for PSG testing after home trial; among those who did not return, nearly 40% were due to discomfort with the device.[7]

Contraindications

- Severe breathing disorders including hypercapnic respiratory failure, respiratory muscle weakness, bullous lung disease (as seen in some types of emphysema), bypassed upper airway, pneumothorax, pneumomediastinum, etc.
- Severe heart disease (including heart failure).
- Pathologically low blood pressure.

- An acute upper respiratory (including nasal, sinus or middle ear) inflammation or infection, or perforation of the ear drum.

Warnings

- Assessment of effectiveness and follow-up testing and evaluation should be conducted to ensure adequate treatment effect.
- Patients who experience an allergic reaction to any part of the device should discontinue use and consult a physician.
- Patients who are unable to breathe through their mouth or experience excessive discomfort when breathing through the device should discontinue use and consult a physician.
- Provent should not be used in patients with hypercapnic respiratory failure. A clinical study has shown that Provent Therapy can result in a moderate but stable increase in PCO2 in some users.
- Patients who develop nasal, sinus or ear infection or inflammation should discontinue use and consult a physician.
- Patients who experience severe nose bleed should discontinue use and consult a physician.
- Patients who develop skin or mucosal irritation, rash, sores, or other discomfort in or around the nose should discontinue use and consult a physician.

Precautions

- Patients should be instructed to breathe through their mouth while falling asleep.
- The safety and effectiveness of Provent Therapy in pregnant women, children under the age of 18, and patients with central sleep apnea have not been established.
- Patients should not use any single Provent Nasal Device for longer than one sleep cycle (e.g., overnight). The Provent Nasal Device is intended for single use only and should be disposed of after use.
- Reuse of the Provent Nasal Device will weaken the adhesive, resulting in an inadequate seal and reduced effectiveness of the device.
- Patients should not use the Provent Nasal Device if they have any sores, abrasions, or skin or mucosal irritation on or around the nose.

Look-Alike/Sound-Alike (LASA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion.

Table 6: Look-alike/Sound-alike Error Risk Potential

Product Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Provent	None	None	None	Proventil Provenge Prevident ProAir Provisc

Comparative Cost

Refer to VA pricing sources for update to date cost information.

Conclusions

Preliminary data suggests that use of Provent significantly improves the AHI and other select OSA outcomes in patients with mild, moderate and severe OSA, compared with baseline values. The device was well tolerated and patient self-reported adherence to the device by was high.

Limitations of the evidence include: most data came from short and mid-term use, small sample size, fair number of drop-outs, large number of exclusion criteria, only one study included a control (sham) group; although in other trials, patients did serve as their own controls.

Robust randomized controlled trials are needed to evaluate the effectiveness of the device compared with established treatments for OSA, and to determine its long-term effectiveness. A small trial comparing Provent to CPAP or placebo device has been recently completed (data not available at this time). Patients are also being recruited for a trial comparing Provent to dental appliances. However, both trials are of short duration.

References

1. Berry RB, Kryger MH, Massie CA. A novel nasal expiratory positive airway pressure (EPAP) device for the treatment of obstructive sleep apnea: a randomized controlled trial. Sleep 2011; 34 (4): 479-485.

2. Kryger MH, Berry RB, Massie CA. Long-term use of a nasal expiratory positive airway pressure (EPAP) device as a treatment for obstructive sleep apnea (OSA). J Clin Sleep Med 2011; 7 (5): 449-453.

3. Rosenthal L, Massie CA, Dolan DC, et al. A multicenter, prospective study of a novel nasal EPAP device in the treatment of obstructive sleep apnea: efficacy and 30-day adherence.

4. Walsh JK, Griffin KS, Forst EH, et al. A convenient expiratory positive airway pressure nasal device for the treatment of sleep apnea in patients non-adherent with continuous positive airway pressure. Sleep Medicine 2011: 12; 147-152.

5. Adams G. Retrospective case series analysis of a nasal expiratory positive airway pressure (EPAP) device to treat obstructive sleep apnea in a clinical practice. SLEEP 2011 Annual Conference.

6. Adams G. Nasal expiratory positive airway pressure (EPAP) device to treat obstructive sleep apnea in medicare aged patients (age ≥65). SLEEP 2012 Annual Conference.

7. Hwang D, Becker K, Chang J, et al. Nasal EPAP as a major OSA therapeutic option in a clinical sleep center setting. SLEEP 2011 Annual Conference

8. Patel AV, Hwang D, Masdeu MJ et al. Predictors of response to a nasal expiratory resistor device and its potential mechanisms of action for treatment of obstructive sleep apnea. J Clin Sleep Med 2011; 7 (1): 13-22.

9. White DP. Auto-PEEP to treat obstructive sleep apnea. J Clin Sleep Med 2009; 5: 538-539.

10. Epstein LJ, Kristo D, Strollo PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2009; 5: 263-276.

11. Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. Mayo Clin Proc 2011; 86(6):549-555.

Appendix 1: Clinical Trials (published)

Study	Inclusion/Exclusion Criteria	Treatment arms	Demographics/Baseline Information	Results
Berry 2011 R, DB, sham-controlled N=250 3-months ITT population: completed week 1 sleep studies (n=229)	**Inclusion** ≥18 years old Diagnosis of OSA AHI≥ 10 (on diagnostic PSG performed within last 3 months) **Exclusion** Use of any device that interferes with nasal/oral breathing; persistent blockage of one or both nostrils preventing air flow; chronic sores or lesion inside or outside nose; chronic nasal decongestant use; O2 sat < 75% or > 10% of diagnostic PSG; O2 sat < 75% for >25% of 1st 4 hours of diagnostic PSG; prior or near-miss MVA in past 12 months due to sleepiness; current use of medications that affect neurocognitive function and/or alertness; h/o allergic reaction to acrylic-based adhesives; h/o of frequent or poorly treated nasal allergies or sinusitis; other sleep disorders that could affect sleepiness scales; use of supplemental 02; h/o CPAP use; h/o of oral appliance use or surgery for OSA; currently working night or rotating shifts; daily consumption of >10 caffeinated or > 3 alcoholic beverages; cardiovascular disease**; h/o of severe or unstable respiratory disease; smokers whose habit interferes with overnight PSG; chronic neuro disorders affecting neurocognitive abilities; current psychiatric illness; illicit drug use	EPAP (n=127) Sham (n=123)	Values for EPAP and sham respectively **Age (yrs):** 47.7±13.4; 46.8±12.0 **Male (%):** 71.4; 65.5 **BMI (kg/m2):** 32.6±7.0; 33.8±6.5 **Baseline AHI (median [range]):** 13.8 [5.3, 22.6]; 11.1 [4.8, 21.8] **Baseline ESS score:** 9.9±4.7; 9.6±4.9	See table below

	EPAP		Sham	
	Device-off	**Device-on**	**Device-off**	**Device-on**
AHI (week 1)	13.8(5.2, 22.6)	5.0(1.7, 11.6) *†	11.1(4.8, 21.8)	11.6(4.0, 21.0)
AHI (month 3)	14.4(5.5, 21.4)	5.6(2.1, 12.5)*†	10.2 (3.4, 19.3)	8.3 (4.2, 20.6)
AHI NREM‡	13.8(6.3, 20.4)	5.3(2.4, 14.6) †	9.9(6.2, 21.2)	8.8(4.6, 23.5)
AHI REM‡	25.3(13.1, 51.9)	11.7(4.3, 31.8)*†	20.9(8.4, 44.7)	20.2(8.2, 45.7)
AHI supine§	26.2(14.9, 48)	12.3(3.7, 28.8) *†	21.8 (14.3, 39)	21.2 (13.5, 44)
AHI non-supine§	8.1 (1.9, 13.3)	2.8 (1.2, 7.2)†	4.9 (2.2, 9.8)	4.3 (1.7, 8.5)
ODI (week 1)	13.7(7.8, 23.6)	7.3(3.5, 13.8)*†	14.6 (8.7, 22.3)	12.2 (6.5, 22)
ODI (month 3)	12.6(7.1, 23.8)	8.6 (3.7, 13.5)*†	13.3(7.5, 23.1)	12.7(6.4, 21.2)
%TST SpO2 <90% (week 1)	1.5(0.2, 5.1)	0.6 (00, 1.7)*†	2.2 (0.2, 6.2)	1.0 (0.2, 4.7)
%TST SpO2 <90% (month 3)	1.3(0.2, 5.0)	0.7 (0.0, 3.5)*†	1.8(0.3, 5.1)	1.8(0.1, 6.2)
TST (min)	363.3±65.3	347.4±69.0†	347.7±76.9	346.2±72.7
Arousal index	17.2 (10.0, 23.8)	17.3 (11.5, 25.4)	16.5 (10.3, 23.9)	15.6 (12.8, 23.1)
Sleep architecture	Stage N1 sleep reduced and stage N increased (device-on vs. off). No significant change in other sleep stages.			
AHI by OSA severity				
Mild (n=38)	8.8	3.9†	N/A	N/A
Moderate (n=36)	20.2	8.4†		
Severe (n=18)	48.2	18.9†		

	EPAP	Sham
Dropouts (n) Week 1/Month 3	8/19	13/15
AHI ≥50% reduction or AHI reduced to < 10/h (% pts.) Week 1/Month 3	62.0/50.7	27.2/22.4
Nights device worn for entire night (%)††	88.2 (67.5, 96.4)	92.3 (84.0, 97.5)
ESS score	7.2±4.2*†	8.3±5.1†
ESS score in those with baseline ≥ 10**	7.9†	11.3

Values shown as median (25, 75 quartiles)
*Significant vs. sham
†Significant device on vs. device off
††Based on patient completed diaries
‡ N=66 (EPAP); N=55 (sham) for AHI REM/NREM
§n=39 (EPAP); 38 (sham) for AHI supine/non-supine
**baseline value was approx 13

Appendix 1-cont.

<table>
<tr><th>Study</th><th>Inclusion/Exclusion Criteria</th><th>Treatment arms</th><th>Demographics/Baseline Information</th><th>Results</th></tr>
<tr>
<td>Kryger 2011

Single arm, open label extension of Berry et al.

N=41 (analyzable cohort n=34)

12 months</td>
<td><u>Inclusion</u>
≥50% reduction in AHI (between device-on at month 3 and device-off at week 1) <u>OR</u> 3-month device-on AHI < 10
Used EPAP device ≥ 4h/night, 5/7 nights/week on average during months 1 and 2 of parent study
Continued use of EPAP does not pose safety risk per study physician/investigator

<u>Exclusion</u>
Same as parent study</td>
<td>All patients received EPAP</td>
<td>Age (yrs): 50.1±13.6
Males (%): 63.4
BMI (kg/m2): 32.5±7.5
AHI: 15.7
ODI: 12.6
Arousal index: 23.9
ESS score: 11
AHI NREM: 12.6 (6.0, 22.2)
AHI REM: 16.8 (5.7, 53.0)
AHI supine: 22.0 (93, 41.9)
AHI non-supine: 3.2 (1.8, 10.3)
TST (min): 365±61.6
Values shown as median (25, 75 quartiles) or mean±SD</td>
<td>
<table>
<tr><th></th><th>EPAP</th></tr>
<tr><td>Dropouts (n)</td><td>7</td></tr>
<tr><td>AHI</td><td>4.7*</td></tr>
<tr><td>AHI NREM (n=30)
AHI REM (n=30)</td><td>2.9 (1.2, 8.3)*
3.7 (0.9, 14.4)*</td></tr>
<tr><td>AHI supine (n=21)
AHI non-supine (n=21)</td><td>6.5 (2.5, 20.1)*
0.8 (0.0, 1.7)*</td></tr>
<tr><td>ODI</td><td>7.6*</td></tr>
<tr><td>Arousal index</td><td>19.0*</td></tr>
<tr><td>TST (min)</td><td>349.3±79.2</td></tr>
<tr><td>Sleep architecture</td><td>Significant increase in stage N2 sleep (change not clinically significant)</td></tr>
<tr><td>Snoring</td><td>Median time reduced by 74.4%*</td></tr>
<tr><td>ESS score</td><td>6*</td></tr>
<tr><td>ESS score in those with baseline ≥ 11† (n=19)</td><td>7*</td></tr>
<tr><td>Device worn entire night (% nights)</td><td>89.3 (81.8, 95.2)</td></tr>
</table>
Values shown as median (25, 75 quartiles)
*Significant vs. baseline
†baseline value was 14
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<td>Walsh 2011

N=59 (43 included in data analysis)

<u>Study stages</u>
-Up to 3 days on each resistance level (week 1)
-Approx 10 days on preferred or assigned resistance
-Approx 5-6 weeks for those meeting efficacy criteria after second PSG</td>
<td><u>Inclusion</u>
≥18 years old
Current signs and symptoms of OSA
Refused or discontinued or minimally adherent (use <3h/night) to CPAP treatment
AHI > 15 or AHI > 10 with evidence of excessive daytime sleepiness, impaired cognition/mood, or HTN

<u>Exclusion</u>
Persistent blockage of one or both nostrils, frequent and/or poorly treated severe nasal allergies or sinusitis, chronic sores or lesion of the nose, chronic use of nasal decongestants, severe respiratory or CV disorders, severe cardiac rhythm disturbance, pathologically low BP, sleep disorders other than OSA, psychiatric disorder with psychotic features, night shift work, excessive caffeine intake, use of other devices interfering with nasal/oral breathing</td>
<td>EPAP with expiratory flow resistance of 50 cmH2O/L/s at flow rate of 100ml/s

EPAP with expiratory flow resistance of 80 cmH2O/L/s at flow rate of 100ml/s

Patient tried both devices for up to 3 days then chose the resistance level they preferred to continue for remainder of trial. Those with no preference were assigned a resistance level.</td>
<td>Age (yrs): 53.7±10.9
Males (%): 62.8
BMI (kg/m2): 34.9±6.7
AHI: 43.3±29
ODI: 38.8±27.2
%TST SpO2 <90%: 13.6±19.3
Arousal index: 50.3±23.3
ESS score: 12.5±5.1
AHI NREM: 41.7±29.8
AHI REM: 55.6±34.5
AHI supine: 66.1±34.6
AHI non-supine: 34.3±31.9</td>
<td>
<table>
<tr><th></th><th colspan="2">All patients (n=43)</th><th colspan="3">Patients meeting efficacy criteria (n=24)</th></tr>
<tr><th></th><th>Off-device</th><th>On-device (10 days)</th><th>Off-device</th><th>On-device (10 days)</th><th>On-device (5 weeks)</th></tr>
<tr><td>AHI</td><td>43.3±29</td><td>27.0±27*</td><td>31.9±20</td><td>11.0±8*</td><td>16.4±12*</td></tr>
<tr><td>AHI NREM</td><td>41.7±30</td><td>24.9±27*</td><td>29.6±21</td><td>8.9±9*</td><td>14.3±14*</td></tr>
<tr><td>AHI REM</td><td>55.6±35</td><td>42.4±29*</td><td>47.2±30</td><td>27.9±21*</td><td>28.2±19*</td></tr>
<tr><td>AHI supine</td><td>66.1±35</td><td>46.6±42*</td><td>54.4±33</td><td>24.8±27*</td><td>32±30*</td></tr>
<tr><td>AHI non-supine</td><td>34.3±32</td><td>19.0±26.*</td><td>21.6±20</td><td>5.5±6*</td><td>8.7±11*</td></tr>
<tr><td>ODI</td><td>38.8±27</td><td>25.6±25*</td><td>27.9±18</td><td>11.3±8*</td><td>17.0±11*</td></tr>
<tr><td>%TST SpO2 <90%</td><td>13.6±19</td><td>9.7±20*</td><td>5.3±4.8</td><td>1.5±2*</td><td>2.2±2</td></tr>
<tr><td>Arousal index</td><td>50.3±23</td><td>40.7±22*</td><td>43.1±17</td><td>30.8±14*</td><td>31.2±14*</td></tr>
<tr><td>TST (min)</td><td>378.4±50</td><td>362±8±66</td><td>375±59</td><td>359.7±81</td><td>376.4±54</td></tr>
<tr><td>Sleep efficiency (%)</td><td>82.1±8</td><td>78.9±12*</td><td>81.7±9</td><td>78.3±15</td><td>82.4±8</td></tr>
<tr><td>ESS score</td><td>11.8‡</td><td>12.2±6‡</td><td>11.1±5</td><td>-</td><td>8.7±4*</td></tr>
</table>
Results are combined for R50 and R80
*Significant vs. without EPAP
‡Values shown are for the subgroup not meeting efficacy criteria
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Appendix 1: cont.

Study	Inclusion/Exclusion Criteria	Treatment arms	Demographics/Baseline Information	Results
Rosenthal 2009 ITT (n=34) 28 completed full protocol	**Inclusion** Adults who snored, had witnessed apneas, or OSA diagnosis Completed at least 1 night in sleep lab AHI > 5 **Exclusion** Prior use of CPAP; uncontrolled serious illness; comorbid sleep disorders; h/o frequent and/or poorly treated severe nasal allergies; sinusitis; difficulty breathing through nose, persistent blockage of one or both nostrils	Pts. underwent 4 nights of PSG with each of the following: control, R50, R80, R110 Pt. continued EPAP (algorithm used to select optimum resistance level) for 30days 30-night in-home portion R50 (n=14) R80 (n=10) R110 (n=5)	**Age (yrs):** 49.8±10.2 **Males (%):** 82.4 **BMI (kg/m2):** 30.1±5.9 **AHI:** 24.5±23.6 **ODI:** 11.0±17.5 **AHI REM:** 30.6±25.7 **% sleep time snoring:** 27.5±23.2 **Sleep efficiency (%):** 77.8±15 **ESS score:** 8.7±4.0	**First 4 nights at each level of resistance** AHI: 13.6±19.6 (R50)*,12.5±18.8 (R80)*, 14.4±19.7 (R110)* **30-night in-home use** **Avg. of initial treatment (R50, R80, R110)** / **Final therapy** AHI: 13.5±18.7* / 15.5±18.9* AHI ≥50% reduction: N/A / 14/34 (41%) REM AHI: 17.2±18.9* / 19.0±21.1* ODI: 8.9±14.0 / 9.2±14.3 % sleep time snoring: 11.6±13.7* / 14.6±20.6* Sleep efficiency (%): 77.4±12 / 75.2±16.2 Sleep architecture: No significant difference between control, initial treatment and final treatment nights ESS score: N/A / 6.9±4.4* *Significant vs. control night

**NYHA III/IV HF, CAD with angina or MI or stroke in past 6 months, cardiac rhythm disturbance (5-beat run of VT, bradycardia if < 30bpm for 10 sec run, untreated atrial fibrillation or Mobitz II or 3rd degree heart block), uncontrolled HTN (SBP > 180mmHg or DBP > 105mmHg), uncontrolled hypotension (SBP <80mmHg or DBP < 55mmHg)

Abbreviations: AHI=apnea-hypopnea index; EPAP= expiratory positive airway pressure; ESS=Epworth Sleepiness Scale; mITT=modified intention to treat; NREM=non Rapid Eye Movement; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; PSG=polysomnography; SpO2=arterial oxygen saturation; TST=total sleep time

Appendix 2: Retrospective Studies (presented as abstracts)

Author	Design	Population	Acclimated to EPAP after 10-day in home trial and returned for PSG n/N (%)	Apnea-hypopnea Index (AHI)			Other AHI assessments	Non-AHI Endpoints		
					Baseline	EPAP			Baseline	EPAP
Adams	Retrospective case series	CPAP failures or current CPAP users	98/131 (75)	All (96) Mild (26) Moderate (35) Severe (35)	25.8 11.5 23.9 48.7	4.2 3.4 4.2 5.6	**% pts. w/ AHI ↓ <5/<10** 56.3/80.7 (all) 63.9/90.6 (mild-mod OSA)	Not applicable		
Adams	Retrospective analysis	Age ≥65	73/91 (80.2)	All (73) Mild (16) Moderate (28) Severe (28) AHI supine AHI non-supine	26.3 11.5 22.6 52.5 35.5 15.6	4.7 5.5 4.1 5.6 9.6 1.6	**% pts. w/ AHI ↓ <5/<10** 54.2/82.6 (all) 59.1/90.2 (mild-mod OSA)	%TST <90% SaO2 Arousal Index TST (min) Sleep efficiency (%)	1.9 31.9 291.5 77.1	0.4 17.6 295.5 79.1
Hwang	Retrospective analysis Kaiser Permanente	CPAP intolerant	49/100 (49)	All (49) AHI supine AHI non-supine	23.8 37.2 12.4	8.0 18.6 2.9	**AHI ↓ 50% and ≤15** All: 36/49 (73.4%) Mild OSA: 15/20 (75%) Mod OSA: 8/12 (67%) Severe OSA: 13/17 (76%)	ODI %TST <90% SaO2 Min. saturation (%)	21.5 14.5 79.9	11.3 9.4 82.8

*In both trials by Adams, concomitant therapies (e.g., positional therapy, chinstrap) was used in 44 and 33 patients in each of the trials respectively