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Research Article

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Improvements in quality of life in female obstructive sleep apnea patients using a gender specific positive airway pressure device

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Abstract

Study Objectives: Females with obstructive sleep apnea (OSA) have more flow limitation, lower apnea-hypopnea index (AHI), shorter apneas, and less severe oxygen desaturations than males. A female-specific auto-adjusting continuous positive airway pressure (fAPAP) algorithm has been developed to target these characteristics. This study investigated the effects of fAPAP therapy on quality of life (QoL) in women with OSA.

Methods: Female patients with AHI ≥ 15/h were eligible. Participants underwent polygraphy or polysomnography. The primary endpoint was change from baseline in Functional Outcomes of Sleep Questionnaire (FOSQ) score after 3 months' fAPAP (AutoSet for Her, ResMed). Secondary endpoints included other sleep-related and QoL questionnaires.

Results: A total of 122 patients were enrolled in the study (age 53.7 ± 9.5 years, body mass index 32.8 ± 6.2 kg/m^2, apnea-hypopnea index [AHI] 39.0 ± 18.2/h); 111/122 completed the study. There was a significant improvement ($p<0.0001$) in FOSQ score from baseline (15.0 ± 3.3) to 3 months (16.9 ± 3.2). Significant improvements were also seen in the Patient Health Questionnaire-9 score (12.3 ± 6.0 *vs.* 7.2 ± 5.4), Epworth Sleepiness Scale score (10.8 ± 4.9 *vs.* 7.3 ± 4.7), EuroQol (EQ)-5D Index score (0.636 ± 0.248 *vs.* 0.763 ± 0.210), EQ-5D visual analogue scale score (54.4 ± 21.7 *vs.* 64.5 ± 21.5) (all $p<0.0001$), and Changes in Sexual Functioning Questionnaire score (38.7 ± 9.5 *vs.* 42.4 ± 8.5; $p=0.001$). In patients with PSG data, fAPAP improved other respiratory parameters (AHI, oxygen desaturation index, oxygen saturation; all $p<0.0001$), and increased time spent in rapid eye movement (REM) sleep (39.7 ± 24.0 *vs.* 48.1 ± 24.5 min; $p=0.022$). Average daily fAPAP usage was 4.8 ± 2.0 h/night.

Conclusion:
Usage of fAPAP significantly improved QoL and increased REM sleep, with good treatment compliance.

Keywords

Obstructive sleep apnea; Female; Quality of life; Sexual function; Continuous positive airway pressure

Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by upper airway closure during sleep, resulting in disrupted breathing and arousals. Moderate to severe OSA (apnea-hypopnea index [AHI] ≥ 15/h) is present in 4-23% of the female population [1,2], and may impact as many as 26% of females aged between 20-70 years [1-3].

There are well known gender differences in OSA. This includes both clinical manifestations and impact on quality of life (QoL). Females often do not present with classic OSA symptoms, such as snoring, obesity and difficulty staying awake during the day. Instead females with OSA may complain of depression, anxiety, mood disturbance, reduced QoL, insomnia and fatigue [4-7]. The presence of OSA in women appears to increase the risk of developing diabetes, dementia and cardiovascular diseases [8-10]. Female sexual health may also be impacted by OSA, although this has not yet been fully explored. A recent study found that females with OSA had significantly more sexual distress and sexual dysfunction compared to those without OSA [11].

The severity of OSA also often differs between genders, with polysomnography (PSG) data showing that females have less severe OSA with overall lower AHI, shorter apneas, and a higher likelihood of rapid eye movement (REM)-only events [12-15]. Younger women in particular often have more episodes of upper airway resistance rather than obstructive apneas.

Continuous positive airway pressure (CPAP) is considered the gold standard treatment for OSA. CPAP applies a fixed pressure that acts as a pneumatic splint to the upper airway, preventing collapse. Auto-adjusting CPAP (APAP) devices monitor breathing on a breath-by-breath basis and respond by delivering the appropriate pressure throughout the night. Effective CPAP treatment in adherent patients has been shown to improve sleepiness and QoL and reduce cardiovascular risk [16-18]. However, the majority of clinical trials of CPAP have included predominantly male participants. Indeed, patient populations in studies during the development and validation of early APAP devices were typically 100% male [19-21]. Only one study to date has examined QoL changes in an entirely female population of OSA patients treated with CPAP [22].

A female-specific APAP (fAPAP) treatment algorithm has been developed with the goal of optimally treating the characteristics of OSA in women. Compared with existing APAP devices, fAPAP is more sensitive in recognizing and increasing pressure in response to flow limitation [23]. A new respiratory effort-related arousal (RERA) detection algorithm alerts clinicians to ongoing problems with respiratory arousals. The fAPAP algorithm protects against strings of REM-based events by introducing an individualized nightly minimum pressure to prevent repeated obstructions. The fAPAP algorithm is designed to increase comfort for users by slowing the rate of pressure increases and decreases, and keeping the overall pressure lower, while still being efficacious [24]. Use of fAPAP has been shown to effectively control AHI while reducing residual flow limitation

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and lowering 95th percentile pressure in female OSA patients during a two-night study [24], but longer term improvements in symptoms have not been determined.

This study investigated changes in symptoms and sleep parameters in female OSA patients during 3 months' treatment with fAPAP.

Materials and Methods

Study design

This prospective, observational, open-label, single cohort study was conducted at one sleep clinic in Spain and two sleep clinics in Germany. The study was approved by local ethics committees and all participants provided informed consent

Patients

Female patients who presented to the sleep clinic with suspected OSA were screened for OSA as per the usual clinical routine (home polygraphy (PG) in Spain or in-lab polysomnography (PSG) in Germany). Eligible patients were those aged ≥18 years who had an AHI of ≥15/h on diagnostic testing. Participants were excluded from the study if they were unable to complete a one-hour CPAP run in. Additional exclusion criteria included: current use or experience with CPAP; use of supplemental oxygen; pregnancy or planned pregnancy in the next 3 months; pre-existing lung disease or condition predisposing to pneumothorax.

Procedures and assessments

At the first study visit, tolerance of CPAP was assessed with a one-hour run in on therapy. Baseline data, including height, weight, age, blood pressure and comorbidities, were collected from patients continuing in the study. Participants were then asked to complete the following questionnaires, with assistance from the nurse/clinician if required: Functional Outcomes of Sleep Questionnaire (FOSQ); Patient Health Questionnaire (PHQ-9); Epworth Sleepiness Scale (ESS); Changes in Sexual Function Questionnaire (CSFQ); and EuroQol 5D (EQ-5D). Patients also provided information on subjective sleep quality based on a Likert scale from 0 (worst) to 10 (best).

Participants were then initiated on fAPAP therapy (AutoSet for Her; ResMed), with humidification and an appropriately fitting mask, and instructed to use fAPAP every night while sleeping for the next 3 months. All participants were phoned during the first weeks of therapy to troubleshoot any issues. If necessary, the participant was invited back to the clinic for a face-to-face visit. All participants returned to the clinic after one month for a visit. During this visit study staff reviewed device usage and attempted to resolve any problems that the participant was experiencing.

Three months after initiation of CPAP, participants returned to the clinic for a final visit. Patient data were downloaded from the device for analysis, including usage, AHI, mask leak, and pressures. At this time participants completed all questionnaires again. In addition, patients in Germany underwent an on-treatment PSG

Endpoints

The primary endpoint was change in QoL during fAPAP based on the FOSQ. Secondary endpoints included change in QoL and sexual function based on other questionnaires, change in sleep quality at 3 months versus baseline based on PSG data, and change in other respiratory parameters at 3 months versus baseline.

Sample size

Sample size was determined based on the results of the CATNAP-trial [25], which showed an unadjusted mean change in FOSQ total score from baseline to week 8 in the modified intention-to-treat population of 0.98 ± 2.89. To achieve power of 80% at α=0.05 it was calculated that a total of 71 patients would be required to detect an increase in FOSQ total score in this study. Assuming a drop-out rate of approximately 10%, the target minimum sample size was set at 80 participants.

Statistical analysis

Differences in baseline characteristics and study endpoints between Germany and Spain were assessed using the t-test or Wilcoxon-Mann-Whitney test for continuous parameters, and Fisher's exact test for categorical parameters. All study results were presented combined because pool-ability was confirmed (i.e. it was determined that there was no significant difference between the countries with respect to the primary study endpoint [change in FOSQ]). Primary and secondary endpoints are displayed separately when significant differences were detected.

Demographic data, baseline characteristics, medical history, medications, baseline PG/PSG data, CPAP data, device usage and QoL endpoints for combined data were summarized descriptively. Number evaluated, mean, standard deviation (SD), median, minimum and maximum were generated for continuous variables. Number evaluated proportion of patients and 95% confidence intervals (CI) were calculated for categorical variables.

Changes in quality of life scores from baseline to 3 months were analyzed for combined data using a paired t-test, testing the null hypothesis that there is no change in QoL scores. Wilcoxon paired signed rank tests were also generated when a non-parametric test was warranted. For comparison of EQ-5D dimensions between baseline and 3 months, a Mantel-Haenszel test was performed with modified ridit scores. All statistical analyses were performed using SAS version 9.4.

Results

Study population

A total of 122 patients (25 from Spain and 97 from Germany) were enrolled in the study (age 53.7 ± 9.5, body mass index [BMI] 32.8 ± 6.2, 56% with hypertension) (Table 1). The majority of patients (74%) used an AirFit P10 for Her mask as the device interface (Table 1). Of the 122 enrolled patients, 111 completed the study.

Participants from Spain and Germany were similar for most baseline characteristics, but those from Spain versus Germany had a significantly higher BMI (36.0 ± 7.8 *vs.* 31.9 ± 5.5 kg/m^2; p=0.02), and were significantly more likely to have comorbid insomnia (36% *vs.* 9%; p=0.002), anxiety (44% *vs.* 3%; p<0.0001) or depression (36% *vs.* 7%; p=0.001).

Questionnaire results

The change in FOSQ total score for participants in Spain versus Germany was not significantly different (2.6 ± 3.7 *vs.* 1.8 ± 3.2; p=0.31), thus primary and secondary endpoints are presented as pooled results. FOSQ total score (primary endpoint) improved significantly from baseline to 3 months (Table 2). Significant improvements from

Table 1. Baseline characteristics of the study population.

Parameter	Spain (N=25)	Germany (N=97)	p-value
Age (years)			
n	25	97	0.371
Mean ± SD (median)	52.1 ± 8.6 (54.0)	54.1 ± 9.8 (55.0)	-
Min, Max	39, 68	25, 76	-
BMI (kg/m²)			
n	25	95	0.021
Mean ± SD (median)	36.0 ± 7.8 (35.0)	31.9 ± 5.5 (32.0)	-
Min, Max	22, 51	18, 49	-
Systolic blood pressure (mmHg)			
N	25	91	0.081
Mean ± SD (median)	137.6 ± 13.7 (140.0)	143.7 ± 19.5 (142.0)	-
Min, Max	110, 165	100, 214	-
Diastolic blood pressure (mmHg)			
N	25	91	0.071
Mean ± SD (median)	87.0 ± 11.0 (90.0)	92.7 ± 14.4 (94.0)	-
Min, Max	70, 114	11, 122	-
Comorbidities n/N (%):			
Heart disease	2/25 (8.0%)	2/97 (2.1%)	0.19[3]
Hypertension	12/25 (48.0%)	56/97 (57.7%)	0.38[3]
Diabetes	2/25 (8.0%)	9/97 (9.3%)	1.00[3]
Anxiety	11/25 (44.0%)	3/97 (3.1%)	<0.0001[3]
Depression	9/25 (36.0%)	7/97 (7.2%)	0.0007[3]
Insomnia	9/25 (36.0%)	9/97 (9.3%)	0.002[3]
Other	22/25 (88.0%)	33/97 (34.0%)	<0.0001[3]
Mask Type, n/N (%)			
AirFit N10 for Her	1/25 (4.0%)	0/97 (0.0%)	<0.0001[3]
AirFit N10	11/25 (44.0%)	1/97 (1.0%)	-
Mirage FX For Her	0/25 (0.0%)	1/97 (1.0%)	-
AirFit P10 for Her	13/25 (52.0%)	95/97 (97.9%)	-

Independent samples t-test; 2. Wilcoxon-Mann-Whitney test; 3. Fisher's exact test (or Chi-square where applicable).

Table 2: Change in questionnaire scores after 3 months' female-specific auto-titrating positive airway pressure therapy.

	Baseline	fAPAP (3 months)	Change from baseline	p-value
FOSQ total score	(n=121)	(n=111)	(n=110)	-
Mean ± SD (range)	15.0 ± 3.3 (6–20)	16.9 ± 3.2 (6–20)	1.9 ± 3.3 (–14, 13)	<0.0001
PHQ-9 total score	(n=119)	(n=111)	(n=108)	-
Mean ± SD (range)	12.3 ± 6.0 (1–27)	7.2 ± 5.4 (0–24)	–5.0 ± 4.9 (–16, 5)	<0.0001
ESS score	(n=122)	(n=108)	(n=108)	-
Mean ± SD (range)	10.8 ± 4.9 (1–24)	7.3 ± 4.7 (0–20)	–3.6 ± 5.0 (–20, 6)	<0.0001
CSFQ total score	(n=87)	(n=70)	(n=63)	-
Mean ± SD (range)	38.7 ± 9.5 (21–63)	42.4 ± 8.5 (22–63)	2.4 ± 5.9 (–12, 16)	0.001
EQ-5D index score	(n=115)	(n=108)	(n=102)	-
Mean ± SD (range)	0.64 ± 0.25 (0.1–1.0)	0.76 ± 0.21 (0.1–1.0)	0.12 ± 0.21 (–0.4, 0.6)	<0.0001
EQ-5D health status (VAS score)	(n=108)	(n=110)	(n=98)	-
Mean ± SD (range)	54.4 ± 21.7 (5–100)	64.5 ± 21.5 (7–100)	9.7 ± 21.5 (–45, 75)	<0.0001

Note: CSFQ: Changes in Sexual Function Questionnaire; ESS, Epworth Sleepiness Scale; fAPAP: female-specific auto-titrating positive airway pressure; FOSQ: Functional Outcomes of Sleep Questionnaire; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; VAS: visual analog scale

baseline were also seen in total scores for the PHQ-9, ESS, CSFQ, indexed EQ-5D (based on country-specific reference values), and EQ-5D health status visual analog scale (Table 2). When individual EQ-5D dimensions were assessed, patients reported a significant improvement in their ability to perform usual activities, significantly fewer participants reported extreme pain or discomfort at 3 months compared with baseline, and patients also reported significant improvements in the Anxiety and Depression dimension after 3

months' fAPAP therapy (Table 3).

Improvements in the majority of secondary outcome questionnaires were similar in the Spanish and German subgroups. The exception was the ESS score, which improved to a significantly greater extent in Spain versus Germany (mean ± SD change from baseline to 3 months of -6.9 5.7 (median -4) *vs.* -2.7 ± 4.4 (median –3); p=0.002).

None of the mean questionnaire scores reached normal population values after 3 months of fAPAP, but changes from baseline were greater than the minimal clinically important difference (MCID) (Table 4).

Respiratory and sleep parameters

Patients from the Spanish center had OSA diagnosed using PG. Baseline PG data and device data after 3 months of fAPAP in these patients are shown in Table 5. OSA and related respiratory events were largely eliminated in all patients. Participants enrolled in Germany underwent full PSG at baseline and after 3 months of fAPAP. There were no significant changes in total sleep time, sleep efficiency or time in slow wave sleep from baseline to 3 months, but the time spent in stage 1 sleep decreased significantly and time in REM sleep was significantly increased (Table 6). Combined 3-month device data from all participants showed that OSA was effectively treated (AHI 1.3 ± 1.7/h, respiratory event-related arousals 0.2 ± 0.5/h) with low mean mask leak (2.4 ± 4.1 L/min, range 0–23). The 95th percentile pressure was 10.2 ± 1.8 cm H_2O.

Device usage

For the 111 patients who completed the study, average device usage was 4.8 ± 2.0 h/night (median usage 5.1 h/night), and 75% of patients used their device for at least 4 h/day (Table 7). For those calculations, zero hours usage was assumed for the duration of the study in patients who stopped using the device prior to the 3-month visit, providing a conservative estimate of device usage. In analyses that included only days where the device was used, average device usage was 5.2 ± 1.9 h/night (median 5.5 h/night) and 83% of patients used their device for at least 4 h/day. There was a trend towards greater use of the fAPAP device in Spain versus Germany (calculated average usage 5.5 ± 1.4 *vs.* 4.6 ± 2.2 h/day); findings were similar for the proportion of days with usage >4 hours (78.2 ± 21.4 *vs.* 63.1 ± 31.6%).

Subjective sleep quality

Subjective sleep quality improved from baseline after fAPAP

Table 3: Change in EuroQol 5D dimensions after 3 months' female-specific auto-titrating positive airway pressure therapy.

Dimension; n (%)	Baseline	fAPAP (3 months)	p-value*
Mobility	**(n=116)**	**(n=109)**	
No problems in walking about	91 (78.4)	89 (81.7)	
Some problems in walking about	25 (21.6)	20 (18.3)	0.55
Confined to bed	0	0	
Self-care	**(n=117)**	**(n=111)**	
No problems with self-care	108 (92.3)	106 (95.5)	
Some problems with washing or dressing	9 (7.7)	5 (4.5)	0.32
Unable to wash or dress myself	0	0	
Usual activities	**(n=117)**	**(n=111)**	
No problems performing usual activities	64 (54.7)	78 (70.3)	
Some problems performing usual activities	51 (43.6)	32 (28.8)	0.02
Unable to perform usual activities	2 (1.7)	1 (0.9)	
Pain/discomfort	**(n=115)**	**(n=110)**	
No pain or discomfort	22 (19.1)	32 (29.1)	
Moderate pain or discomfort	64 (55.7)	69 (62.7)	0.002
Extreme pain or discomfort	29 (25.2)	9 (8.2)	
Anxiety/depression	**(n=115)**	**(n=111)**	
Not anxious or depressed	40 (34.8)	57 (51.4)	
Moderately anxious or depressed	62 (53.9)	49 (44.1)	0.005
Extremely anxious or depressed	13 (11.3)	5 (4.5)	

Note: fAPAP: female-specific auto-titrating positive airway pressure.
*p-values generated using Mantel-Haenszel test with modified ridit scores.

Table 4: Questionnaire scores in relation to healthy populations and minimal clinically important difference.

Questionnaire	Healthy population scores	Baseline score (mean ± SD)	fAPAP (3 months) (mean ± SD)	Change from baseline with fAPAP	MCID
FOSQ	≥ 17.9	15.0 ± 3.3	16.9 ± 3.2	1.9 ± 3.3	0.75
ESS	≤ 9	10.8 ± 4.9	7.3 ± 4.7	–3.6 ± 5.0	2–3
PHQ-9	≤ 4	12.3 ± 6.0	7.2 ± 5.4	–5.0 ± 4.9	5
CSFQ	47.8 ± 9	38.7 ± 9.5	42.4 ± 8.5	2.4 ± 5.9	Unknown
EQ-5D Index	1	0.636 ± 0.248	0.763 ± 0.210	0.12 ± 0.21	0.074

Note: CSFQ: Changes in Sexual Function Questionnaire; ESS, Epworth Sleepiness Scale; fAPAP: female-specific auto-titrating positive airway pressure; FOSQ: Functional Outcomes of Sleep Questionnaire; MCID: minimal clinically important difference; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation.

Table 5: Respiratory data at baseline (polygraphy) and 3 months (device) for patients from Spain.

	Baseline	**fAPAP (3 months)**
	(n=25)	**(n=23)**
AHI, /h	39.2 ± 20.5 (17–76)	0.9 ± 0.7 (0–3)
ODI, /h	39.8 ± 21.5 (13–79)	-
RERA, /h	-	0.2 ± 0.3 (0–1)
OAI, /h	8.2 ± 10.6 (0–36)	0.3 ± 0.3 (0–1)
CAI, /h	0.4 ± 1.1 (0–5)	0.2 ± 0.3 (0–1)
Mean SaO_2, %	97.1 ± 1.6 (92–99)	-
Minimum SaO_2, %	77.3 ± 8.3 (52–88)	-
Total sleep time, min	381.5 ± 56.5 (273–486)	-
Mean leak, L/min	-	3.8 ± 3.8 (0–16)
95th percentile leak, L/min	-	18.7 ± 8.2 (5–35)
Median pressure, cmH_2O	-	9.1 ± 1.4 (7–11)
95th percentile pressure, cmH_2O	-	11.0 ± 1.1 (9–13)

Note: Values are mean ± standard deviation (range).
AHI: apnea-hypopnea index; CAI: central apnea index; fAPAP: female-specific auto-titrating positive airway pressure; OAI: obstructive apnea index; ODI: oxygen desaturation index; RERA: respiratory event-related arousals; SaO_2: oxygen saturation.

Table 6. Polysomnography data at baseline and 3 months for patients from Germany.

	Baseline (n=97)	**fAPAP (3 months) (n=87)**	**p-value**
Respiratory parameters			
AHI, /h	39.0±17.7 (14-100)	3.3±6.0 (0-50)	<0.0001
ODI, /h	19.1±18.0 (1-86)	4.3±7.0 (0-56)	<0.0001
OAI, /h	27.2±34.4 (0-289)	0.9±2.4 (0-14)	<0.0001
CAI, /h	1.1±3.1 (0-27)	1.2±3.0 (0-25)	0.03
Basal SaO_2, %	93.5±2,2 (87-97)	94.6±2.2 (89-98)	<0.0001
Minimum SaO_2,%	79.9±8.3 (53-95)	86.7±4.8 (69-96)	<0.0001
Sleep parameters			
Total sleep time, min	321.0±63.9 (160–568)	326.5±72.2 (116–478)	0.80
Sleep efficiency, %	79.4±12.6 (34–99)	79.7±14.7 (25–99)	0.91
Time in S1 sleep, min	39.1±38.1 (5–260)	29.4 ± 25.2 (3–150)	0.02
Time in S2 sleep, min	197.2±57.9 (38–326)	193.4±49.0 (25–296)	0.50
Time in SWS, min	40.0±26.3 (0–132)	47.0±29.4 (0–113)	0.07
Time in REM sleep, min	39.7±24.0 (0–142)	48.1±24.5 (0–110)	0.02

Values are mean ± standard deviation (range).
AHI: apnea-hypopnea index; CAI: central apnea index; fAPAP: female-specific auto-titrating positive airway pressure; OAI: obstructive apnea index; ODI: oxygen desaturation index; REM: rapid eye movement; SaO_2: oxygen saturation; SD: standard deviation; SWS: slow-wave sleep.

Table 7:. Device usage (completed cases).

	fAPAP (3 months)
	(n=111)
Average usage, h/day	4.8 ± 2.0 (0.1–8.2)
Days with usage >4 h/day, %	66.2 ± 30.4 (1.9–100.0)
Average usage ≥ 4 h/day, n (%)	75 (67.6)

Note: Values are mean ± standard deviation (range) or number of patients (%). fAPAP: female-specific auto-titrating positive airway pressure.

Table 8: Subjective sleep quality.

	Baseline	**fAPAP (3 months)**	**Change from baseline**	**P value**
How easy/difficult was it to fall asleep?	(n=120)	(n=107)	(n=106)	
Mean ± SD (range)*	5.2 ± 2.9 (0–10)	6.3 ± 2.5 (0–10)	1.1 ± 2.7 (–5, 7)	<0.0001
How well did you feel like you slept most nights?	(n=119)	(n=109)	(n=107)	
Mean ± SD (range)*	3.5 ± 2.4 (0–10)	6.1 ± 2.3 (1–10)	2.6 ± 2.7 (–3, 8)	<0.0001
How refreshed did you feel in the mornings on waking?	(n=120)	(n=108)	(n=107)	
Mean ± SD (range)	2.4 ± 2.0 (0–10)	6.3 ± 2.4 (0–10)	3.8 ± 3.0 (–5, 10)	<0.0001
On average, how many times did you wake up each night? n (%)	(n=119)	(n=109)		
None	7 (5.9)	19 (17.4)		<0.0001**
2-Jan	43 (36.1)	58 (53.2)		
4-Mar	56 (47.1)	31 (28.4)		
6-May	12 (10.1)	1 (0.9)		
More than 6	1 (0.8)	0		

*Score on a scale from 0 (worst) to 10 (best) **Mantel-Haenszel test (modified ridit scores) SD: Standard Deviation

therapy, as did the number of hours patients reported that they slept each night (Table 8).

Discussion

This is the first appropriately-powered study to examine the impact of a new female-specific APAP device on QoL in female OSA patients. The results showed that APAP therapy using a female-specific algorithm was associated with improvements in a range of QoL measures.

Our population was, on average, middle-aged and moderately obese with a moderate level of sleepiness at baseline and low levels of anxiety and depression. The primary endpoint, FOSQ score, improved significantly from baseline during the 3-month study in this group of women. Weaver et al. described a FOSQ score cut-off value of ≥ 17.9 as being normal [26]. Based on this, the proportion of patients with normal FOSQ values at baseline in our study was 23%. After treatment, this had increased to 53%, but 47% of patients still had FOSQ scores below normal. These results are similar to another study of CPAP patients, where only 35% of patients had normal scores after treatment [27]. The MCID for the FOSQ is 0.75. The average improvement in our patient group during fAPAP therapy was 1.9 points. Thus, although QoL was not normalized in all patients, improvements were of a magnitude that would result in a relevant improvement in clinical symptoms. Clinically relevant improvements (based on the MCID) were also seen in the ESS, PHQ-9 and EQ-5D index scores in our study, while the CSFQ score MCID has not yet been defined.

We used the CSFQ in this study to better explore the area of female sexual heath and function in OSA. In men, untreated OSA is associated with erectile dysfunction and low sexual hormone levels, which are improved by treatment with CPAP [28]. However, there are comparatively few data on the implications of OSA for female sexual health. Two small questionnaire-based studies in female patients (n=22 and n=25) found that women with OSA score lower on sexual function questionnaires compared with controls [29,30]. One study found that women with untreated OSA (n=80), regardless of severity, were at higher risk of having sexual difficulties, and rated higher on the sexual dysfunction and sexual distress scales than a population-based sample of women without OSA [11]. In the current study, we also showed that females with OSA rated lower than the population average on the CSFQ. During the conduct of our study, it was emphasized that completion of the CSFQ was optional. This was done to avoid any feelings of embarrassment for participants. The response rate to the CSFQ was significantly lower than the other questionnaires. Therefore, future studies will need to carefully consider the methodology used to collect female sexual function information. Our findings that the CFSQ score improved from outside the normal range to the lower end of what might be considered normal, suggest that fAPAP has the potential to improve sexual function in female patients with OSA. Increases in the CFSQ score reached statistical significance versus baseline, and this beneficial effect of fAPAP warrants further investigation.

The questionnaires used in our study had been validated in both the German and Spanish languages. Therefore, it is reasonable to conclude that the improvements reported between countries were referring to the same symptoms. However, we did see some regional differences. At baseline, patients from Spain had a higher BMI and reported more sleepiness, anxiety and depression than those from Germany, although rates in Germany were particularly low compared with similar studies [4-7]. They also showed a significantly greater improvement in sleepiness (ESS score). It is possible that the higher BMI in the Spanish group was responsible for the higher levels of sleepiness, anxiety and depression, as obesity is associated with these symptoms even in the absence of OSA [31]. Greater sleepiness at baseline may also have meant greater potential to improve. In addition, device usage was greater in the Spanish group (average 5.5 ± 1.4 *vs.* 4.6 ± 2.2 h/night; p=0.02), which may have been due to the higher levels of baseline sleepiness, and also may have contributed to the greater improvement in sleepiness seen in this group. It has been suggested previously that CPAP usage for ≥ 5 h/night is required to achieve significant improvements in daytime sleepiness, a finding supported by our results.

Only one previous clinical study focused on QoL in female-only CPAP users [22]. Campos-Rodriguez et al. used the Quebec Sleep Questionnaire as a primary endpoint, plus the Hospital Anxiety and Depression scale (HADS), the abbreviated Profile of Mood Stages (POMS), and the Short Form Health Survey (SF-12), none of which were used in our study. Our questionnaires were selected, in part, due to the availability of validation in both the German and Spanish languages. Despite the different questionnaires used, the study by Campos-Rodriguez et al. reported significant improvements in all QoL measures in females using fixed CPAP compared with the control group, consistent with our findings. In addition, both studies showed a similar improvement in ESS scores during CPAP therapy (by 3 points in the Campos-Rodriguez et al. study and 3.6 points on average in this study). The findings of these two trials strengthen the limited pool of data evaluating females during CPAP therapy [22].

Women in our study showed adequate compliance with fAPAP therapy, with mean daily usage of 4.8 ± 2.0 hours. Generally, device usage of >4 h/night is considered acceptable. An analysis of female CPAP compliance published in 2013 found that females were generally compliant with CPAP, with 79.9% still using CPAP after 10 years and median usage of 6 h/day [32]. In our study population, median usage of fAPAP was nearly as high, at 5.5 h/day in Spain and 4.6 h/day in Germany.

Use of fAPAP in our study resulted in patients spending significantly less time in stage one sleep and significantly more time in REM sleep compared with baseline, as measured by PSG in Germany. Time spent in slow wave sleep was also increased, but this did not reach statistical significance. REM sleep is thought to be important for consolidation of procedural memories, while slow wave sleep may help patients feel rested and benefit declarative memories [33].

The focus of this study was on determining the efficacy of fAPAP therapy. Therefore, ability to tolerate a CPAP run-in, provision of ongoing support, and one-month follow-up for all patients were part of the study design. This is not the standard clinical pathway in every country, therefore the results may not be widely generalizable. Another important limitation of this study was its design (single cohort rather than randomized trial) and the resulting lack of a comparator group (e.g. APAP with a standard, rather than female-specific, algorithm). It is therefore not possible to categorically state that the improvements in QoL that occurred during fAPAP treatment were due to optimization of therapy based on the female-specific algorithm or whether standard APAP therapy would have had similar effects. Future research should focus on effectiveness

of fAPAP treatment compared with other forms of positive airway pressure therapy.

Conclusion

In conclusion, this study showed significant improvements in QoL in female OSA patients treated for 3 months with a female-specific APAP device. This included improvements in sexual function, which have been rarely studied in these patients. The female-specific algorithm evaluated in this study represents one approach to targeting therapy for individual patients (personalized medicine). The availability of therapeutic options that take into account differences in the physiology and presentation of OSA in women could have the potential to improve outcomes for these patients.

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References

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, et al. (2013) Increased Prevalence of Sleep-Disordered Breathing in Adults. Am J Epidemiol 1779: 1006-1014.
2. Young T, Evans L, Finn L, Palta M (1997) Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 20: 705-706.
3. Franklin KA, Sahlin C, Stenlund H, Lindberg E (2013) Sleep apnoea is a common occurrence in females. Eur Respir J 41: 610-615.
4. Lee MH, Lee SA, Lee GH, Ryu HS, Chung S, et al. (2014) Gender differences in the effect of comorbid insomnia symptom on depression, anxiety, fatigue, and daytime sleepiness in patients with obstructive sleep apnea. Sleep Breath 18: 111-117.
5. Quintana-Gallego E, Carmona-Bernal C, Capote F, Sánchez-Armengol Á, Botebol-Benhamou G, et al. (2004) Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. Respir Med 98: 984-989.
6. Shepertycky MR, Banno K, Kryger MH (2005) Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep 28: 309-314.
7. Ye L, Pien GW, Ratcliffe SJ, Weaver TE (2009) Gender differences in obstructive sleep apnea and treatment response to continuous positive airway pressure. J Clin Sleep Med 5: 512-518.
8. Greenberg-Dotan S, Reuveni H, Simon-Tuval T, Oksenberg A, Tarasiuk A (2007) Gender differences in morbidity and health care utilization among adult obstructive sleep apnea patients. Sleep 30: 1173-1180.
9. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, et al. (2011) Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 306: 613-619.
10. Campos-Rodriguez F, Martinez-Garcia M, Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, et al. (2012) Cardiovascular mortality in women with OSA with or without CPAP treatment- A cohort study. AnnInternMed 156: 115-122.
11. Petersen M, Kristensen E, Berg S, Giraldi A, Midgren B (2011) Sexual function in female patients with obstructive sleep apnea. J Sex Med 8: 2560-2568.
12. O'Connor C, Thornley KS, Hanly PJ (2000) Gender differences in the polysomnographic features of obstructive sleep apnea. Am J Respir Crit Care Med 161: 1465-1472.
13. Ye L, Pien G, Ratcliffe S, Weaver T (2009) Gender differences in Obstructive Sleep Apnea and Treatment Responses to Continuous Positive Airway Pressure. J Clin Sleep Med 5: 512-518.
14. Mohsenin V (2001) Gender differences in the expression of sleep-disordered breathing: role of upper airway dimensions. Chest 120: 1442-1447.
15. Valencia-Flores M, Bliwise DL, Guilleminault C, Rhoads NP, Clerk A (1992) Gender differences in sleep architecture in sleep apnoea syndrome. J Sleep Res 1: 51-53.
16. Gay P, Weaver T, Loube D, Iber C (2006) Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 29: 381-401.
17. Lewis EF, Wang R, Punjabi N, Gottlieb DJ, Quan SF, et al. (2017) Impact of continuous positive airway pressure and oxygen on health status in patients with coronary heart disease, cardiovascular risk factors, and obstructive sleep apnea: A Heart Biomarker Evaluation in Apnea Treatment (HEARTBEAT) analysis. Am Heart J 189: 59-67.
18. Marin JM, Carrizo SJ, Vicente E, Agusti AGN (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. The Lancet 365: 1046-1053.
19. Rees K, Wraith PK, Berthon-Jones M, Douglas NJ (1998) Detection of apnoeas, hypopnoeas and arousals by the AutoSet in the sleep apnoea/ hypopnoea syndrome. Eur Respir J 12: 764-769.
20. Teschler H, Wessendorf TE, Farhat AA, Konietzko N, Berthon-Jones M (2000) Two months auto-adjusting versus conventional nCPAP for obstructive sleep apnoea syndrome. Eur Respir J 15: 990-995.
21. Teschler H, Berthon-Jones M, Thompson AB, Henkel A, Henry J, et al. (1996) Automated continuous positive airway pressure titration for obstructive sleep apnea syndrome. Am J Respir Crit Care Med 154: 734-740.
22. Campos-Rodriguez F, Queipo-Corona C, Carmona-Bernal C, Jurado-Gamez B, Cordero-Guevara J, et al. (2016) Continuous Positive Airway Pressure Improves Quality of Life in Women with OSA. A Randomized-controlled Trial. Am J Respir Crit Care Med 15:1286-1294
23. Isetta V, Montserrat JM, Santano R, Wimms AJ, Ramanan D, et al. (2016) Novel Approach to Simulate Sleep Apnea Patients for Evaluating Positive Pressure Therapy Devices. PLoS One 11: e0151530.
24. McArdle N, King S, Shepherd K, Baker V, Ramanan D, et al. (2015) Study of a Novel APAP Algorithm for the Treatment of Obstructive Sleep Apnea in Women. Sleep 38: 1775-1781.
25. Weaver TE, Mancini C, Maislin G, Cater J, Staley B, et al. (2012) Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. Am J Respir Crit Care Med 186: 677-683.
26. Weaver TE (2007) Relationship Between Hours of CPAP Use and Achieving Normal Levels of Sleepiness and Daily Functioning. Sleep 30: 711-719.
27. Antic NA, Catcheside P, Buchan C, Hensley M, Naughton MT, et al. (2011) The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. Sleep 34: 111-119.
28. Zhang XB, Lin QC, Zeng HQ, Jiang XT, Chen B, et al. (2016) Erectile Dysfunction and Sexual Hormone Levels in Men With Obstructive Sleep Apnea: Efficacy of Continuous Positive Airway Pressure. Arch Sex Behav 45: 235-240.
29. Yilmaz Z, Sirinocak PB, Voyvoda B, Ozcan L (2017) Sexual Dysfunction in Premenopausal Women With Obstructive Sleep Apnea. Urol J 14: 5051-5056.
30. Koseoglu N, Koseoglu H, Itil O, Oztura I, Baklan B, et al. (2007) Sexual function status in women with obstructive sleep apnea syndrome. J Sex Med 4: 1352-1357.
31. Araghi MH, Jagielski A, Neira I, Brown A, Higgs S, et al. (2013) The complex associations among sleep quality, anxiety-depression, and quality of life in patients with extreme obesity. Sleep 36: 1859-1865.
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