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SCIENTIFIC INVESTIGATIONS

Dose-response relationship between positive airway pressure therapy and excessive daytime sleepiness: the HomePAP study

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Study Objectives: The clinical benefits of positive airway pressure (PAP) therapy for obstructive sleep apnea are assumed to require adherent PAP usage, defined by the Centers for Medicare & Medicaid Services as ≥ 4 hours of use ≥ 70% of nights. However, this definition is based on early data and does not necessarily capture improvements at subthreshold adherence. We explored dose-response relationships between PAP adherence measures and excessive daytime sleepiness from the HomePAP randomized controlled trial.

Methods: Participants aged ≥ 18 years with an apnea-hypopnea index ≥ 15 events/h and baseline sleepiness (Epworth Sleepiness Scale [ESS] ≥ 12) received PAP therapy. Data were collected at baseline, 1-month follow-up, and 3-months follow-up. Regression models and receiver operating characteristic curves evaluated PAP measures as predictors of ESS change and normalization (ESS < 10).

Results: In 119 participants (aged 49.4 ± 12.6 years, 66.4% male, 72.3% White), > 50% were PAP nonadherent per Centers for Medicare & Medicaid Services criteria at 3 months. The percentage of nights with PAP use ≥ 4 hours predicted ESS change ($P = .023$), but not when controlling for the apnea-hypopnea index. The percentage of nights with ≥ 4 hours and average PAP use provided the best discrimination for predicting ESS normalization; each 10% increase in PAP use ≥ 4 hours increased the odds of ESS normalization by 22% ($P = .007$); those using PAP ≥ 4 hours had a nearly 3-fold greater odds of ESS normalization ($P = .025$). PAP use for at least 4 hours and on 70% of nights provided the best balance between specificity (0.50) and sensitivity (0.73).

Conclusions: Although subadherent PAP usage may still confer some benefit for patients with obstructive sleep apnea, adherence to current criteria confers the highest likelihood for ESS change and normalization.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Portable Monitoring for Diagnosis and Management of Sleep Apnea (HomePAP); URL: https://clinicaltrials.gov/ct2/show/NCT00642486; Identifier: NCT00642486.

Keywords: PAP therapy, adherence, excessive daytime sleepiness, Epworth Sleepiness Scale, HomePAP trial

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Data from the HomePAP randomized controlled trial were leveraged to explore dose-response relationships between several positive airway pressure (PAP) adherence measures and excessive daytime sleepiness using the Epworth Sleepiness Scale to better elucidate thresholds of adherence for significant therapeutic benefit and inform guidelines for PAP therapy use.

Study Impact: Although patients with fewer hours of PAP use still may benefit, clinicians may expect to see significant Epworth Sleepiness Scale change/normalization in patients using PAP ≥ 4 hours per night ≥ 70% of nights. An adherence variable accounting for self-reported sleep duration was not superior in predicting outcomes.

INTRODUCTION

Positive airway pressure (PAP) therapy is the gold-standard treatment for moderate-to-severe obstructive sleep apnea (OSA), a highly prevalent sleep-related breathing disorder. PAP therapy has been shown to reduce OSA symptoms and related health risks,[1] especially in regard to improving excessive daytime sleepiness (EDS), a debilitating symptom for many patients. In its 2019 clinical practice guidelines,[2] the American Academy of Sleep Medicine identified EDS as a critical outcome of OSA therapy and strongly recommended the use of PAP therapy for improving alertness. The Epworth Sleepiness Scale (ESS), a well-validated measure of EDS, is routinely used to assess daytime sleep propensity.[3] Although the ESS does not measure objective sleepiness, or at least the same dimension of sleepiness as that measured by the Maintenance of Wakefulness Test,[4] the ESS was found to be a more discriminating tool for evaluating EDS across sleep disorders populations than the Maintenance of Wakefulness Test or the Multiple Sleep Latency Test.[5] As such, benefit

from PAP therapy can be measured through ESS change and normalization.

PAP therapy benefits are assumed to necessitate adherent PAP usage, defined by the Centers for Medicare & Medicaid Services (CMS) as usage for ≥ 4 hours on ≥ 70% of all nights monitored.[6] This criterion was informed by one of the first studies of PAP adherence defining "regular users" vs "irregular users."[7] The criterion adopted in this early study was based on limited knowledge and data.[8–10] Although there is some support for this threshold for predicting PAP benefits and symptom recurrence,[11] the criterion does not account for linear improvement in outcomes with increasing PAP use below the given threshold.[12]

Several studies have examined adherence criteria,[13,14] and more specifically, the dose-response relationship between PAP use and clinical outcomes. The Weaver, Maislin, et al[12] 2007 landmark investigation found that mean PAP adherence of 4 hours of nightly use was an optimal cutoff for identifying ESS improvement; however, the data were also consistent with a linear dose response with greater benefit with increased nightly duration of use up to 7 hours per night. The Antic et al[15] 2011 investigation was modeled from this study and found similar results. However, neither study evaluated other adherence metrics, such as average PAP use as a percentage of the sleep period, which accounts for sleep duration, along with hours of PAP use, percentage of nights with PAP use, and percentage of nights with ≥ 4 hours of PAP use per night.

We explored dose-response relationships between several PAP adherence measures and EDS using the ESS by leveraging data from the HomePAP multicenter, randomized, controlled trial (RCT).[16] Through analyzing different measures of PAP adherence in relation to changes in sleep propensity, we hoped to better elucidate thresholds of adherence for significant therapeutic benefit and inform guidelines for PAP therapy use.

METHODS

Participants

Participants were aged ≥ 18 years with a high pretest probability of moderate-to-severe OSA and an ESS ≥ 12. Excluded were participants with a pre-existing diagnosis of OSA, significant comorbid pulmonary disease, awake hypercapnia or hypoventilation syndrome, heart failure, neuromuscular disease, drowsy driving, chronic narcotic use, alcohol abuse, uncontrolled psychiatric disorder, clinical features of other sleep disorders, inability to undergo home sleep apnea testing (HSAT), planned upper airway or gastric bypass surgery, or use of supplemental oxygen. Participants were recruited from 7 American Academy of Sleep Medicine–accredited academic sleep centers in the United States: University Hospitals, MetroHealth Medical Center, and Cleveland Clinic, Cleveland, OH; Northwestern University, Chicago, IL; University of Wisconsin, Madison, WI; University of Minnesota, Minneapolis, MN; and University of Washington, Seattle, WA. All participants provided written informed consent. Ethics approval was obtained from each participating center.

Study design and data collection

The details of the protocol, including the provision of standardized OSA education and randomization procedures, have been described previously.[16] An in-laboratory polysomnography study or HSAT was used to obtain the apnea-hypopnea index (AHI)/respiratory event index from participants, and those with values ≥ 15 events/h were included. Participants randomized to in-laboratory polysomnography underwent PAP titration, whereas the HSAT group underwent autotitration for 1 week at home to identify optimal fixed-pressure settings. Criteria for successful titration included ≥ 4 hours of recording with AHI < 10 events/h at optimal pressure (90th percentile pressure setting in segments without a large leak). All participants were provided with a REMStar AutoPro CPAP Unit (Philips Respironics, Murrysville, PA), which included a SmartCard to gather AHI, adherence, and leak data.

Demographic data (age, sex, race, median income by ZIP Code, study site), health data (body mass index, depression diagnosis, anxiolytic and sedative hypnotic use), and ESS scores were collected at baseline, 1-month follow-up, and 3-month follow-up study visits using standardized questionnaires and direct measurement (height, weight). PAP data were collected at the 1-month and 3-month follow-up visits from the SmartCard. We extracted the following data from the download:

1. Proportion of participants with average PAP use ≥ 4 hours on ≥ 70% of nights (categorical, shown as n [%])
2. Proportion of participants with average PAP use ≥ 4 hours per night (categorical, shown as n [%])
3. Percentage of nights with PAP use ≥ 4 hours (continuous, shown as mean % ± standard deviation)
4. Average PAP use per night (continuous, shown as mean minutes ± standard deviation). This value was taken as the average over all nights used.

The following variable was also derived:

5. Percentage of sleep hours with PAP use per night (continuous, shown as mean % ± standard deviation). This variable was defined as recorded hours of use/average self-reported total sleep time. Average total sleep time per night was derived from a questionnaire that asked, "How many hours do you think you actually sleep on average?"

Statistical analysis

Data from participants who underwent both polysomnography and HSAT were aggregated for primary analyses (the AHI and respiratory event index were together referred to as "AHI" for simplicity), although they were separated for some subanalyses. Categorical variables were summarized using frequencies and percentages, and continuous measures were described using means and standard deviations. Linear and logistic regression models were used to evaluate PAP measures as predictors of our outcomes: Both ESS change (continuous, 2-point change, and 4-point change)[17] and ESS normalization (ESS < 10) were evaluated. Receiver operating characteristic curves evaluated the overall predictive ability of continuous adherence measures vs ESS change or normalization based on the area under the curve (AUC). The best cut point was derived based on the

combination of sensitivity and specificity using the Youden Index (sensitivity + specificity – 1). Multivariable linear regression models were fit for ESS change at 1 and 3 months. Multiple imputation using fully conditional specification was used to impute missing data (ie, for depression status and income). Multicollinearity among predictors was assessed using variance inflation factors and condition indices. Final multivariable models included adjustment for race, depression, randomized group, baseline AHI, income by ZIP Code, and baseline ESS. Multivariable models for ESS normalization were only adjusted for baseline ESS because of the low frequency of patients without normalization. Analyses were performed using SAS software (version 9.4; Cary, NC).

RESULTS

Sample characteristics

Characteristics of the 119 participants with complete data (aged 49.4 ± 12.6 years, 66.4% male, 72.3% White) are shown in **Table 1**. Overall, participants were overweight and obese (body mass index 38.3 ± 8.7) but had a range of OSA (AHI 46.9 ± 26.5 events/h) and income by ZIP Code ($57,648.3 ± $19,238.1). Mean ESS was elevated (15.2 ± 3.0).

PAP adherence at follow-up is shown in **Table 2**. PAP use and adherence increased from 1 month to 3 months, reflected in our 2 criteria for adherence and 3 different measurements of utilization. Using traditional criteria for adherence to PAP of ≥ 4 hours on ≥ 70% of nights, 38.2% of participants were adherent at 1 month and 45.4% were adherent at 3 months. Using criteria of an average ≥ 4 hours of use (over all monitored nights), adherence was 49.6% at 1 month and 53.8% at 3 months. Based on the average percentage of nights with PAP use ≥ 4 hours, 54.2% of patients were adherent at 1 month and 57.7% were adherent at 3 months. PAP usage measured by percentage of sleep hours with PAP use per night was 59.4% at 1 month and 62.7% at 3 months, and usage measured by average PAP use per night was 4.09 and 4.29 hours on average at 1 and 3 months, respectively. Looking at the characteristics of participants who were adherent to PAP, those who used PAP ≥ 4 hours per night at 3 months on average had a higher median income by ZIP Code ($59,500 ± $17,200 vs $52,300 ± $20,900; $P = .032$) and AHI (53 ± 28 events/h vs 39 ± 22 events/h; $P = .002$); baseline ESS did not differ between adherence/nonadherence ($P = .70$). The HSAT group reported a greater percentage of nights with PAP use ≥ 4 hours than the PSG group (62.8% of nights vs 49.4%; $P = .018$). No significant differences between adherent/nonadherent groups

Table 2—PAP adherence at 3 months (n = 119).

Factor	Statistics
Average PAP use ≥ 4 h ≥ 70% of nights, n (%)	54 (45.4)
Average PAP use ≥ 4 h, n (%)	64 (53.8)
Percentage of nights with PAP use ≥ 4 h, mean % ± SD	57.7 ± 32.5
Average PAP use per night, mean h ± SD	4.3 ± 2.3
Percentage of sleep h with PAP use per night, mean % ± SD	62.7 ± 29.2

Statistics presented as mean ± SD or n (column %). Data represent adherence over the entire 3-month period. PAP = positive airway pressure, SD = standard deviation.

Table 1—Sample characteristics (n = 119) stratified by ESS normalization.

Factor	Total (n = 119)	No ESS Normalization (n = 24)	ESS Normalization (n = 95)	*P*
Age, y	49.4 ± 12.6	54.4 ± 12.3	48.1 ± 12.4	.028[a]
Sex, male	79 (66.4)	14 (58.3)	65 (68.4)	.35[b]
Race, White	86 (72.3)	16 (66.7)	70 (73.7)	.49[b]
BMI, kg/m^2	38.3 ± 8.7	39.8 ± 10.6	37.9 ± 8.2	.34[a]
Income, $	57,648 ± 19,238	55,111 ± 21,018	58,303 ± 18,817	.47[a]
Depression diagnosis	30 (26.1)	11 (45.8)	19 (20.9)	.013[b]
Anxiolytic use	25 (21.6)	6 (26.1)	19 (20.4)	.55[b]
Sedative-hypnotic use	1 (0.84)	0 (0.0)	1 (1.1)	.99[c]
AHI, events/h	46.9 ± 26.5	32.1 ± 18.6	50.6 ± 27.0	.002[a]
ESS	15.2 ± 3.0	15.8 ± 3.4	15.0 ± 2.9	.29[a]
Eligibility test type				.22[b]
PSG	56 (47.1)	14 (58.3)	42 (44.2)	
HSAT	63 (52.9)	10 (41.7)	53 (55.8)	

Statistics presented as mean ± SD or n (column %). *P* values: [a]ANOVA, [b]Pearson chi-square test, [c]Fisher exact test. AHI = apnea-hypopnea index, ANOVA = analysis of variance, BMI = body mass index, ESS = Epworth Sleepiness Scale, HSAT = home sleep apnea testing, PSG = polysomnography, SD = standard deviation.

and no significant trends based on any adherence criteria were observed with respect to baseline ESS.

Predictors of ESS change and ESS normalization

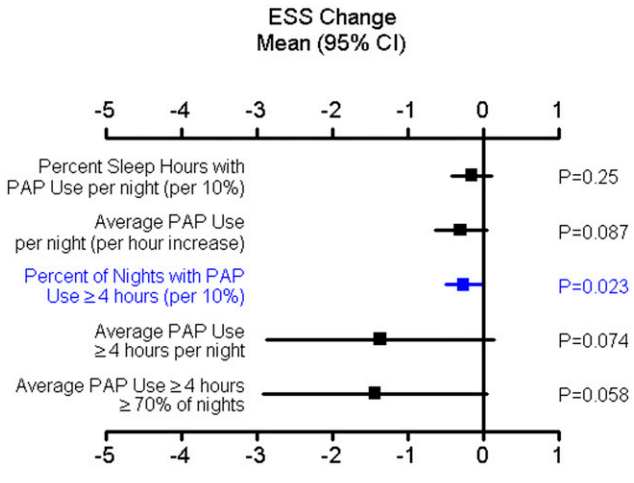
Figure 1 shows the association between PAP adherence and ESS change (both continuously assessed) at 3 months, adjusting for race, depression, randomization group, median income by zip code, and baseline ESS. For each 10% increase in percent nights with PAP use ≥ 4 hours, the total ESS score decreased by 0.27 points ($P = .023$); other adherence measures were not significantly associated with ESS change. However, after also adjusting for AHI, none of the adherence measures were statistically significant predictors of ESS change. A sensitivity analysis (**Table S1** and **Table S2** in the supplemental material) indicated that variation in AHI explained the change in significance because without this factor, significance was similar to what was observed in models just adjusting for baseline ESS.

Figure 2 shows the associations between PAP adherence and ESS normalization (< 10), adjusting for baseline ESS at 3 months. Younger age (ages 48.3 ± 12.5 years vs 54.5 ± 12.1 years; $P = .027$), no diagnosis of depression (79% vs 21%; $P = .006$), and higher AHI (50 vs 31 events/h; $P = .001$) were associated with ESS normalization, but given the small number of patients without normalization (n = 24) we were unable to adjust for all factors simultaneously. Average PAP use per night, percentage of nights with PAP use ≥ 4 hours, and average PAP use ≥ 4 hours per night were all significantly associated with ESS normalization. Each added hour of use increased the odds of normalization by 32% ($P = .013$), whereas participants with an average PAP use ≥ 4 hours had a nearly 3 times greater odds of normalization as compared to participants with an average PAP use < 4 hours ($P = .025$). For each 10% increase in the percentage of nights with PAP use ≥ 4 hours, the odds of ESS normalization increased by 22% ($P = .007$). However, as before, these associations were attenuated after adjusting for baseline AHI. Additional analyses at 1 month showed that AUC was greatest for average PAP use; the probability that participants with a ≥ 2-point ESS change at 1 month had a greater average PAP use than participants who did not have a ≥ 2-point change was 0.69.

Figure 3 shows the receiver operating characteristic curves for the prediction of a ≥ 2-point ESS change at 3 months by PAP adherence (measured from baseline to follow-up). At 3 months, 91.6% of participants had a ≥ 2-point ESS reduction, and the AUCs for the PAP adherence measures were still not significantly different. Relative to the 2-point change, we found that models of 4-point change performed worse with lower AUC measures and less significance when we evaluated the predictive ability of the adherence criteria. Additional analyses at 3 months showed that AUC was greatest for percentage of sleep hours with PAP use; the probability that a participant with normal ESS at 3 months had a greater percentage of sleep hours with PAP use than a participant who had less than a 2-point change was 0.60. Although the associations between different adherence criteria and a ≥ 4-point ESS change at 1 month were evaluated, no significant associations were observed. Overall, discrimination was worse at 1 month than at 3 months, and there was little discrimination between the PAP adherence measures.

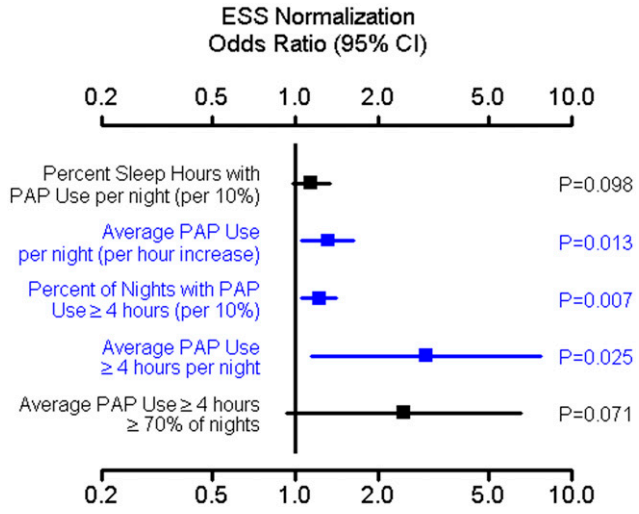
Figure 4 shows the receiver operating characteristic curves for the prediction of ESS normalization at 3 months by PAP adherence. At 3 months, AUC was greatest for percentage of

Figure 1—Forest plot of change in ESS at 3 months by PAP adherence criteria, adjusting for baseline ESS, race, depression, randomized group, and income.



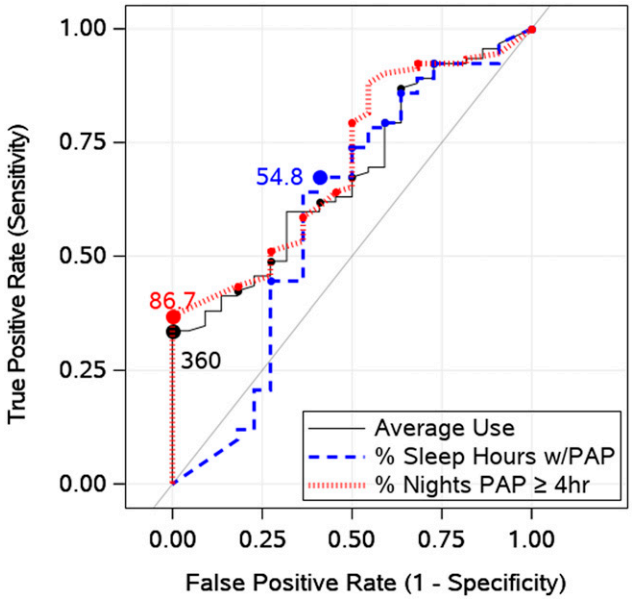
The mean ESS changes stratified by PAP adherence criteria. CI = confidence interval, ESS = Epworth Sleepiness Scale, PAP = positive airway pressure.

Figure 2—Forest plot of odds ratios for ESS normalization at 3 months by PAP adherence criteria, adjusting for baseline ESS.



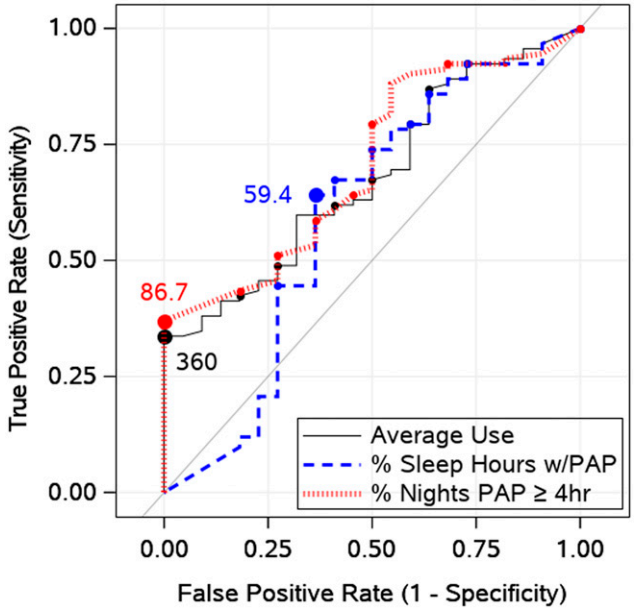
Odds ratios for ESS normalization stratified by PAP adherence criteria. CI = confidence interval, ESS = Epworth Sleepiness Scale, PAP = positive airway pressure.

Figure 3—ROC curves for prediction of ≥ 2-point ESS change at 3 months.



ROC curves for prediction of ≥ 2-point ESS change using 3 PAP adherence criteria. AUCs were 0.60 (95% CI, 0.44–0.75) for "Average Use" (average PAP use), 0.62 (95% CI, 0.46–0.77) for "% Nights PAP ≥ 4 hours" (percentage of nights with PAP use ≥ 4 hours), and 0.53 (95% CI, 0.31–0.75) for "% Sleep Hours w/PAP" (percentage of sleep hours with PAP use per night). Points highlighted reflect the largest combination of sensitivity and specificity (Youden Index). AUC = area under the curve, CI = confidence interval, ESS = Epworth Sleepiness Scale, PAP = positive airway pressure, ROC = receiver operating characteristic.

Figure 4—ROC curves for prediction of ESS normalization at 3 months.



Shown are ROC curves for prediction of ESS normalization using 3 PAP adherence criteria. AUCs were 0.68 (95% CI, 0.56–0.79) for "Average Use" (average PAP use), 0.71 (95% CI, 0.59–0.82) for "% Nights PAP ≥ 4 hours" (percentage of nights with PAP use ≥ 4 hours), and 0.60 (95% CI, 0.44–0.75) for "% Sleep Hours w/PAP" (percentage of sleep hours with PAP use per night). Points highlighted reflect the largest combination of sensitivity and specificity (Youden Index). AUC = area under the curve, CI = confidence interval, ESS = Epworth Sleepiness Scale, PAP = positive airway pressure, ROC = receiver operating characteristic curve.

nights with PAP use ≥ 4 hours; the probability that a participant with a normalized ESS at 3 months used their PAP for a greater percentage of nights with PAP use at ≥ 4 hours than a participant who did not normalize was 0.71. The AUC was 0.68 for average PAP use per night and 0.60 for percentage of sleep hours with PAP use per night; only percentage of sleep hours with PAP use per night significantly differed from the others, providing worse discrimination (worse-than-average use by 0.08, $P = .020$; worse than percentage of nights with PAP use ≥ 4 hours by 0.11, $P = .002$).

Table 3 and **Table 4** show the analysis of hourly cut points for sensitivity and specificity, ie, the probabilities of detecting a ≥ 2-point ESS change and a < 2-point ESS change (**Table 3**), along with ESS normalization and ESS nonnormalization (**Table 4**).

For a ≥ 2-point ESS reduction (**Table 3**), 70% of nights with PAP use ≥ 4 hours provided the best discrimination, with a good balance of sensitivity (0.47) and specificity (0.70) and the second-highest Youden Index (0.17); the highest Youden Index was seen at 90%, which provided poor sensitivity. A similar relationship was seen for average PAP use per night; 240 minutes (4 hours) provided the best balance of sensitivity (0.56) and specificity (0.60) but the second-highest Youden Index (0.16), with 360 minutes (6 hours) providing the best discrimination (specificity 1.00, Youden Index 0.30) but poor sensitivity (0.30), and 180 minutes (3 hours) providing nearly the lowest Youden Index (0.00, lowest -0.11), with poor specificity (0.30). Percentage of sleep hours with PAP use of 60% provided both the best balance of specificity (0.59) and sensitivity (0.60) and the highest Youden Index (0.19). This finding suggests that clinically significant ESS improvement can be expected with current CMS criteria adherence, 4-6 hours average PAP use, or approximately 60% of sleep hours with PAP use.

For ESS normalization (**Table 4**), a level of 70% of nights with PAP use ≥ 4 hours provided the best balance of sensitivity (0.50) and specificity (0.73), but the highest Youden Index was observed at 30% because of high sensitivity. An average PAP use per night of 360 minutes (6 hours) provided the best discrimination (specificity 1.00, Youden Index 0.34) but poor sensitivity (0.34); 240 minutes (4 hours) provided the best balance of sensitivity (0.60) and specificity (0.68), whereas 3 hours provided poorer specificity relative to 4 hours. Looking at both measures of PAP adherence, the current CMS cut points of ≥ 4 hours of PAP use ≥ 70% of nights and average use ≥ 4 hours had poorer discrimination than other cut points but a better balance between specificity and sensitivity. This finding suggests that ESS normalization can be predicted by average PAP use ≥ 4 hours ≥ 70% of nights and average use ≥ 4 hours and that most patients will normalize with use at or above these thresholds.

Table 3—ROC best cut points for prediction of ≥ 2-point ESS change with combined sensitivity and specificity at 3 months.

Factor	Cut Point	Sensitivity	Specificity	Youden Index
Average PAP use, min	60	0.89	0.00	–0.11
	120	0.98	0.20	0.08
	180	0.71	0.30	0.00
	240	**0.56**	**0.60**	**0.16**
	300	0.42	0.70	0.12
	360	*0.30*	*1.00*	*0.30*
	420	0.14	1.00	0.14
	480	0.03	1.00	0.03
Percentage of nights with PAP use ≥ 4 h	10	0.90	0.10	0.00
	20	0.88	0.20	0.08
	30	0.80	0.30	0.10
	40	0.70	0.40	0.10
	50	0.61	0.40	0.01
	60	0.54	0.60	0.14
	70	**0.47**	**0.70**	**0.17**
	80	0.39	0.70	0.09
	90	*0.25*	*1.00*	*0.25*
Percentage of sleep h with PAP use	10	0.93	0.00	–0.07
	20	0.89	0.10	–0.01
	30	0.87	0.20	0.07
	40	0.79	0.30	0.09
	50	0.67	0.40	0.07
	60	***0.59***	***0.60***	***0.19***
	70	0.44	0.60	0.04
	80	0.36	0.70	0.06
	90	0.21	0.70	–0.09

Italicized rows show the highest Youden Index. Bolded rows show the best balance of sensitivity and specificity. ESS = Epworth Sleepiness Scale, PAP = positive airway pressure, ROC = receiver operating characteristic.

DISCUSSION

In this secondary analysis of PAP adherence and ESS using data from the HomePAP multicenter trial we found the following: (1) more than 40% of participants were PAP nonadherent according to CMS criteria, with most nonadherence seen in participants who had lower income (median by ZIP Code) and/or lower AHI; (2) percentage of nights with PAP use ≥ 4 hours predicted ESS change at 3 months; (3) percentage of nights with PAP use ≥ 4 hours and average PAP use over 3 months provided the best discrimination for predicting ESS normalization, with current CMS cut points of 4 hours and 70% of nights providing the best balance between specificity and sensitivity; and (4) percentage of sleep hours with PAP use per night, a novel variable that accounts for individual sleep duration, was not a better predictor of ESS change or normalization than current standards.

Nonadherence to PAP therapy is common, with current rates as high as 60% in some populations.[18] As detailed in the Billings et al[19] 2011 analysis of race and residential socioeconomics as predictors of adherence in the HomePAP sample, despite standardized care and access to treatment, adherence can be particularly challenging for patients living in lower-socioeconomic-level communities. A greater understanding of barriers to PAP therapy in this population is needed.

Of all the adherence criteria evaluated, average use in hours and percentage of nights with PAP use > 3 months were the only significant predictors of ESS change. Our novel calculation of percentage of sleep hours with PAP use was not significantly related to ESS change/normalization. However, this calculation was limited by self-report at baseline, and sleep duration could have changed over time. As such, future investigations using objective sleep duration from actigraphy or wearable devices are warranted. Moreover, our findings suggest that although the highest combination of sensitivity and specificity may be found at the extremes of the distributions, traditional cut points—or values near these cut points—tended to best balance sensitivity and specificity in our cohort.

Note that some of the associations we observed between adherence and change in sleepiness may have been confounded by

Table 4—ROC best cut points for prediction of ESS normalization with combined sensitivity and specificity at 3 months.

Factor	Cut Point	Sensitivity	Specificity	Youden Index
Average PAP use, min	60	0.92	0.18	0.11
	120	0.91	0.27	0.19
	180	0.74	0.41	0.15
	240	**0.60**	**0.68**	**0.28**
	300	0.46	0.77	0.23
	360	*0.34*	*1.00*	*0.34*
	420	0.16	1.00	0.16
	480	0.03	1.00	0.03
Percentage of nights with PAP use ≥ 4 h	10	0.92	0.18	0.11
	20	0.91	0.32	0.23
	30	*0.85*	*0.45*	*0.30*
	40	0.74	0.50	0.24
	50	0.64	0.55	0.19
	60	0.57	0.64	0.20
	70	**0.50**	**0.73**	**0.23**
	80	0.43	0.82	0.25
	90	0.28	1.00	0.28
Percentage of sleep h with PAP use	10	0.95	0.09	0.04
	20	0.92	0.23	0.15
	30	0.89	0.27	0.16
	40	0.82	0.36	0.18
	50	0.71	0.50	0.21
	60	***0.62***	***0.64***	***0.26***
	70	0.46	0.64	0.09
	80	0.37	0.73	0.10
	90	0.21	0.73	–0.07

Italicized rows show the highest Youden Index. Bolded rows show the best balance of sensitivity and specificity. ESS = Epworth Sleepiness Scale, PAP = positive airway pressure, ROC = receiver operating characteristic.

AHI, which is associated with both adherence and ESS change. An association between higher AHI and greater adherence has been observed in other studies and meta-analyses.[20–22] Patients with more severe disease who see more immediate improvements in daytime sleepiness may be more motivated to use PAP therapy.[22] However, the baseline AHI is unlikely to directly influence the change in sleepiness, in contrast to adherence, which will contribute to improvements in sleep and thus sleepiness.

Our finding that percentage of nights with PAP use ≥ 4 hours and average PAP use over an average of 3 months provide the best discrimination complements prior studies that analyzed average hours of use in relation to ESS change/normalization. Even though the cut points of 6 hours and 90% of nights provided the greatest specificity and highest Youden Index values, currently accepted cut points of ≥ 4 hours and ≥ 4 hours ≥ 70% of nights provide the greatest balance between positive and negative predictive values for ESS change/normalization.

Our study strengths include the use of data from a large, prospective trial, enhancing generalizability; our findings of a dose-response relationship between PAP adherence and ESS change/normalization reinforce those of previous studies, mainly suggesting that attempts at improving adherence are likely to improve sleepiness while also supporting some clinical efficacy of even suboptimal adherence on important outcomes, such as sleepiness. We also investigated the effects of adherence measures not previously explored, including percentage of sleep hours with PAP use per night, which accounted for variability in sleep duration and did not prove to be a better predictor of ESS improvement.

However, our study has several limitations. The modest number of individuals from racial/ethnic minorities limited our ability to make inferences across racial/ethnic groups. Furthermore, although the study sample had nonnormal baseline ESS scores allowing for the analysis of ESS normalization, we could not address the effects of PAP therapy on lesser degrees of sleep propensity, including nonsleepy patients. In addition, ESS normalization may not reflect functional status. Notably, the HomePAP study excluded patients with mild OSA. The Youden Index was used to identify the best cut points. This approach equally weights sensitivity and specificity when determining the optimal choice. As such, it may identify points that may not reflect the best clinical practice (eg, very high sensitivity but low specificity). Alternative methods for identifying the best cut points also

have advantages and disadvantages, but in this study using alternative methods generally identified similar cut points as the Youden Index, although they may have led to other optimal choices. It is important that both the Youden Index and observed sensitivity and specificity are evaluated when assessing the value of a given cut point. Finally, unmeasured confounders may have contributed to both PAP adherence and ESS scores.

Overall, through analyzing different measures of adherence in relation to changes in daytime sleep propensity, our results support the use of current PAP adherence criteria. Although patients with fewer hours of PAP use may still benefit from PAP therapy, understanding that disease severity is a key factor in symptom resolution with therapy, clinicians may expect to see significant ESS change and normalization in patients using PAP for an average of ≥ 4 hours per night ≥ 70% of nights. In addition, newer measures that account for objective sleep duration could potentially provide greater insight into expected ESS change/normalization, although further study is needed. Research aimed at identifying and addressing barriers to PAP adherence is of the utmost clinical importance.

ABBREVIATIONS

AHI, apnea-hypopnea index
AUC, area under the curve
CMS, Centers for Medicare and Medicaid
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
HSAT, home sleep apnea testing
OSA, obstructive sleep apnea
PAP, positive airway pressure

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All authors have seen and approved the manuscript. All work for this study was performed at the institutions listed: University Hospitals, MetroHealth Medical Center, and Cleveland Clinic, Cleveland, OH; Northwestern University, Chicago, IL; University of Wisconsin, Madison, WI; University of Minnesota, Minneapolis, MN; and University of Washington, Seattle, WA. Dr. Benca has served as a consultant to Eisai, Genomind, Idorsia, Jazz, Merck, and Sunovion. Dr. Foldvary-Schaefer has research funding from Jazz (unrelated to study), Takeda, and Suven. Dr. Iber has research funding from Inspire Medical. Drs. Kapur and Rosen were board members of the American Academy of Sleep Medicine at the time of submission of this article. They contributed to this article in their personal capacity. The views expressed are their own and do not necessarily represent the views of the American Academy of Sleep Medicine. Dr. Redline has received consulting fees from ApniMed Inc., Lily Inc., Eisai Inc., and Jazz (unrelated to the study) and grants from the National Institutes of Health and Jazz. Dr. Zee has received grants from the National Institutes of Health, Vanda, and Philips Respironics. Maeve Pascoe, Noah Andrews, James Bena, Dr. Auckley and Dr. Billings report no conflicts of interest.