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SCIENTIFIC INVESTIGATIONS

Depression scores improve with continuous positive airway pressure in specialized sleep clinics: real-world data

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Study Objectives: To assess changes in Hospital Anxiety and Depression Scale (HADS) scores after continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea.

Methods: Consecutive patients attending the Alfred Health sleep clinic, diagnosed with obstructive sleep apnea, and prescribed CPAP were recruited. The primary outcome was a change in the HADS depression (HADS-D) and anxiety (HADS-A) subscales from the time of diagnosis to follow-up. Secondary analysis compared high (> 4 hours) and low (< 4 hours) CPAP adherence groups and change in depression cases, defined by HADS-D ≥ 8, and anxiety cases, defined by HADS-A ≥ 11.

Results: We included 108 participants in the final analysis. Adherence groups were well matched in baseline mood, sleepiness, and apnea variables. Overall age (mean ± standard deviation) was 56.1 ± 12.8 years, and there was a median (interquartile ratio) apnea-hypopnea-index of 42.7 (27.5–58.1) or median (interquartile ratio) oxygen-desaturation-index of 43.0 (26.0–74.0). The median duration of CPAP therapy was 1.3 years. The HADS-D decreased after CPAP by –1.4 (adjusted 95% confidence interval, –2.1 to –0.6; $P = .001$). Patients with high-CPAP adherence (n = 84) had a tendency towards a greater reduction in HADS-D (–1.5) compared with those with low-CPAP adherence (n = 24; –0.3; adjusted $P = .19$). Depression cases (HADS-D ≥ 8) decreased by 13.1% in the high-CPAP-adherence group ($P = .03$) and increased by 4.1% in the low-CPAP-adherence group ($P = .71$). The HADS-A decreased after CPAP by –1.8 (adjusted 95% confidence interval, –1.8 to –0.4; $P = .004$). There was no significant difference between adherence groups or anxiety cases (HADS-A > 11).

Conclusions: Specialized obstructive sleep apnea treatment with CPAP reduces depression scores, with a trend toward greater reduction in those with high CPAP adherence.

Keywords: depression, anxiety, obstructive sleep apnea, continuous positive airway pressure

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea and depression are highly prevalent and commonly co-existent disorders, yet the effect of continuous positive airway pressure treatment on depression is not fully understood. To date, few studies have sought to assess this relationship as a primary outcome in real-world patients, with adequate follow-up, using a screening instrument validated in the sleep clinic setting.

Study Impact: This study has found a statistically significant reduction in depression scores after the initiation of continuous positive airway pressure treatment, which is clinically significant in those with high continuous positive airway pressure adherence. These findings suggest that in patients with co-existent obstructive sleep apnea and depression, referral to a sleep clinic and treatment of obstructive sleep apnea should be considered.

INTRODUCTION

Worldwide, depression contributes to a huge burden of disease. It is the single largest contributor to global disability,[1] and as such depression results in alarming morbidity, mortality, and economic costs.[2]

In Australia, the National Health Survey of 2017–2018 found that 10.4% of the population self-reported currently experiencing depression or feelings of depression lasting 6 months or more.[3] This prevalence is more than doubled in patients with obstructive sleep apnea (OSA), with a 2019 meta-analysis estimating that 23% of people with OSA have clinical depression.[4]

OSA is also a highly prevalent disorder. A 2017 meta-analysis of OSA prevalence estimated the prevalence of moderate-to-severe OSA (apnea-hypopnea index > 15 events/h) as 6%–17%.[5]

Both OSA and depression are common and often coexistent disorders[6] that share many overlapping symptoms.[7] They likely share a multidirectional interplay, whereby the presence of one disorder may worsen or lead to treatment resistance in the other.[8,9]

There is uncertainty in the current literature as to whether treating OSA improves mental health outcomes.[10–16] It remains to be seen whether continuous positive airway pressure (CPAP) may in fact reduce depression scores.[10–16] Many of the previous

randomized controlled trials examining this relationship have been limited by a short duration of follow-up (≤ 1 month) [17–28] and small sample size (≤ 50 participants),[17–20,22–27,29] and in a vast majority of the studies, changes in depression scores have been limited to a secondary analysis rather than a primary study endpoint.[10,12,16,20,22–27,29–31] Our study is distinct from other studies that have attempted to address this question in that we have examined changes in depression and anxiety scores after CPAP treatment as a primary outcome in the real-world clinic setting. We have used a tool specifically validated in the sleep clinic population, and we have allowed for adequate follow-up duration and participant numbers.

The primary aim of this study was to assess changes in Hospital Anxiety and Depression Scale (HADS) scores for depression (HADS-D) and for anxiety (HADS-A) pre- and post-CPAP treatment in real-world patients with OSA. Further, we aimed to explore whether CPAP adherence was associated with a change in HADS scores and ultimately a reduction in depression and anxiety cases, as defined by HADS-D ≥ 8 and HADS-A ≥ 11, respectively. The results of our study will provide valuable insight into the ongoing management of OSA and coexistent depression symptoms.

METHODS

Study population

Consecutive patients attending the Alfred Health Sleep Clinic, a university-affiliated tertiary hospital in a large metropolitan city (Melbourne, Australia), were screened and invited to participate if they had diagnosed OSA via a diagnostic sleep study with an HADS completed at the time of the diagnostic study. Subsequent review was by an experienced sleep physician who had recommended a trial of CPAP in addition to usual care, with lifestyle advice on diet, exercise, and healthy sleep practice. Exclusion criteria included patients aged < 18 years, those who did not speak English, those with CPAP therapy duration < 30 days, those with CPAP use before the diagnostic sleep study, or those with a change in psychotropic medications since the diagnostic sleep study. Ethics approval was obtained by the Alfred Hospital institution's human research ethics committee (HREC245/18).

Participants were recruited after commencement of CPAP therapy. The follow-up duration varied for participants. Voluntary informed written consent was obtained. Baseline HADS and Epworth Sleepiness Scale (ESS) scores were obtained at the time of the diagnostic sleep study and were repeated at the time of follow-up. A CPAP device adherence download for the preceding 90 days was obtained at the time of follow-up. Demographic and patient-reported psychiatric details were obtained via questionnaire at the time of follow-up. Physician-reported medical and psychiatric comorbidities were obtained via review of the electronic medical record.

HADS

OSA and depression share many overlapping symptoms,[7] and as such the screening tool for depression used in the sleep clinic population is of utmost importance. Many depression screening tools have been validated in the general population, but few have been validated in the sleep clinic population. The HADS[32] has been validated as a screening tool for depression and anxiety in the sleep clinic population.[33] It is designed to exclude somatic symptoms of depression and thus contains minimal symptoms that overlap with OSA. As such, it has been recommended as a robust screening tool for depression in the sleep clinic population, where clinical psychiatric interview is not feasible.[33,34]

The HADS is a self-administered questionnaire, of which 7 items pertain to depressive symptoms (HADS-D) and 7 items pertain to anxiety symptoms (HADS-A). Each subscale is totaled to a maximum of 21 points. HADS-D ≥ 8 has been shown to represent clinically significant depression, predicting a diagnosis of a major depressive episode with a sensitivity of 83.1% and a specificity of 83.3% (area under the curve, 0.851).[33] Similarly, HADS-A ≥ 11 has been found to represent clinically significant anxiety with a sensitivity of 93.1% and a specificity of 84.7% (area under the curve, 0.911).[33] In our study, patients with HADS-D ≥ 8 were defined as depression cases, and those with HADS-A ≥ 11 were defined as anxiety cases. The minimal clinically important difference for the HADS has been estimated as –1.5 in populations with chronic disease.[35,36]

Diagnostic sleep studies

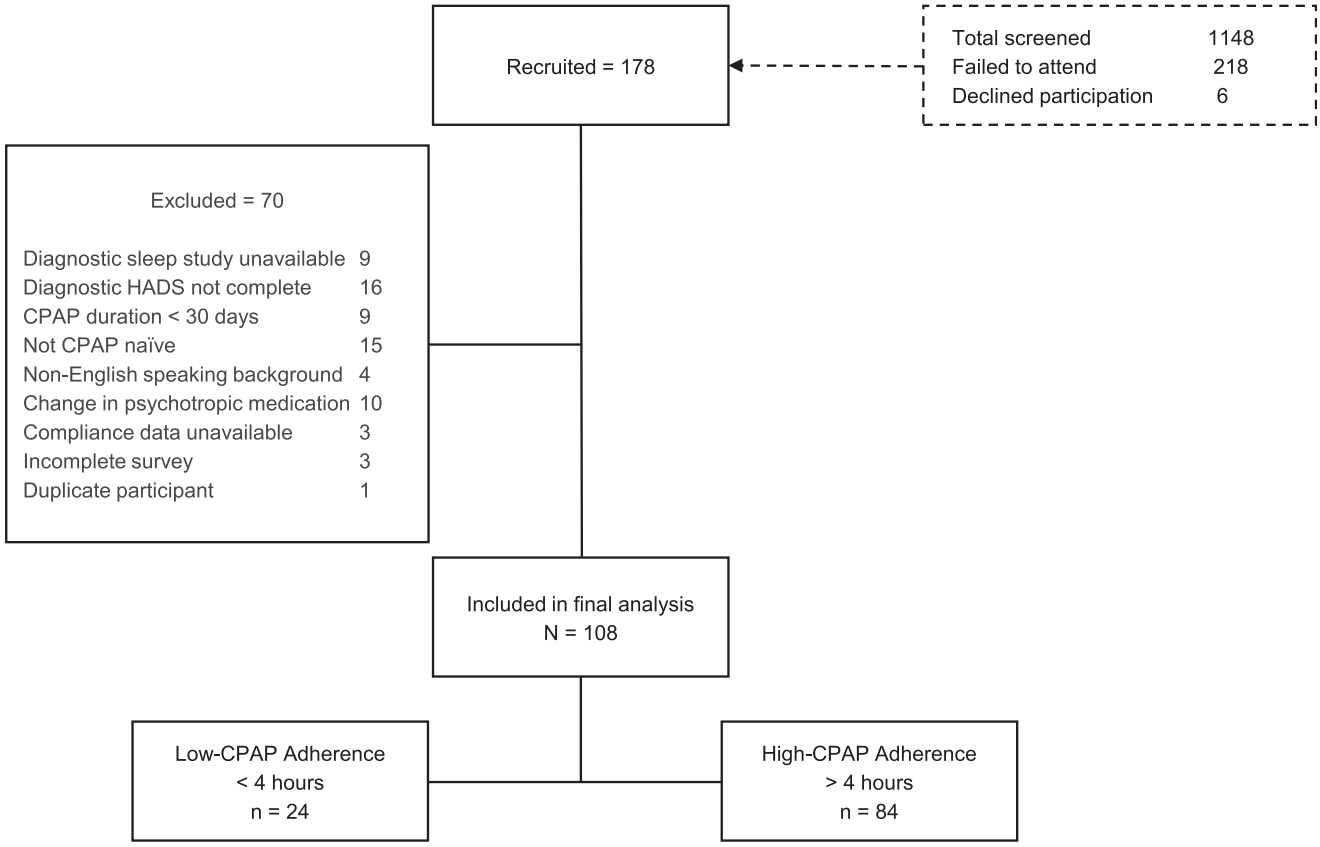
Participants underwent either full-channel in-laboratory polysomnography or single-channel overnight home oximetry at the discretion of the treating physician, based on their comorbidities and pretest probability of OSA. The diagnosis and management of OSA by overnight home oximetry has been found to be comparable to that found by in-laboratory polysomnography in patients with a high pretest probability of moderate to severe OSA.[37,38] Full channel in-laboratory polysomnography was performed with the apnea-hypopnea index calculated as per the American Academy of Sleep Medicine alternative criteria.[39] Overnight home oximetry was conducted in patients with a high pretest probability of moderate to severe OSA using the Masimo Rad 5 oximeter (Irvine, California, USA), with a 2-second averaging time and 0.5 Hz signal acquisition and with the oxygen desaturation index defined as oxygen desaturation > 3% from baseline per hour of recording time. Since 2013, the Alfred Health Sleep Clinic has routinely assessed the HADS in addition to the ESS score and anthropometric measurements with each diagnostic sleep study.

Statistical analysis

The minimal clinically important difference for the HADS is –1.5 as estimated in chronic disease populations; however, the Sleep Apnea Cardiovascular Endpoints study, the largest randomized controlled trial to date in the sleep apnea population, has shown a HADS reduction of 0.8. Therefore, we chose to use a minimal clinically important difference of 1.0.[10,35,36] Power analysis estimated that a sample size of 108 participants was required, using an alpha level of significance of 0.05 with 80% power, with previously published data from our cen-ter estimating a mean HADS-D of 6.1 ± 3.7 in the sleep clinic population.[33]

All data were reported as mean ± standard deviation or median (interquartile range [IQR]) as appropriate for tests of normality. Comparison of characteristics by CPAP adherence

Figure 1—Funnel plot.



CPAP = continuous positive airway pressure, HADS = Hospital Anxiety and Depression Scale.

groups was assessed using the chi-square test or Fisher exact test for binary and categorical data as appropriate, and analysis of variance or Wilcoxon rank sum for continuous data as appropriate.

Univariate and multivariate mixed-effects linear regression was performed to consider the correlation between responses from the same participant over time. For the primary outcome, adjustments were made for the duration of CPAP therapy, baseline mood scores, ESS score, and Charlson-Deyo comorbidity index. Because of low numbers in the secondary analyses of adherence and depression and anxiety cases, these analyses could only be adjusted for the duration of CPAP therapy and baseline mood scores. Statistical difference was defined as $P > .05$ using 2-tailed tests. All statistical analysis was performed using STATA version 15.0 (StataCorp LP, College Station, TX).

RESULTS

Participant characteristics

All case files for the 1,148 patients attending the Alfred Health Sleep Clinic over a 6-month period in 2018 were screened. Of these patients, the majority either did not have OSA or were not prescribed CPAP, 218 failed to attend, and 6 declined, resulting in 108 included in the final analysis (**Figure 1**). The sample was predominantly middle-aged (ages 56.0 ± 12.8 years), overweight (body mass index, 37.7 ± 11.5 kg/m^2), male (72%), and sleepy (ESS score, 9.8 ± 5.6) with a high proportion of medical comorbidities, consistent with the tertiary hospital setting. The excluded participants were similar in age, sex, body mass index, and baseline mood and sleepiness variables to those included in the final analysis, with a mean HADS-D of 6.4 ± 4.3, a HADS-A of 6.7 ± 3.6, and an ESS score of 9.8 ± 5.5.

High CPAP adherence (mean nightly CPAP usage > 4 hours) and low CPAP adherence (< 4 hours) groups were well matched at baseline in demographic, mood, sleepiness, and apnea variables (**Table 1**). The only variable of significance was a higher body mass index of 39.1 kg/m^2 in the high-CPAP-adherence group compared to that in the low-CPAP-adherence group, 33.2 kg/m^2 ($P = .02$).

We found that 18% (20/108) of participants self-reported active or previous cigarette smoking, 56% (61/108) reported any alcohol use, and 3.7% (4/108) reported illicit drug use. In addition, 42% (45/108) of participants were actively employed and 4 participants were shift workers.

Sleep characteristics

Sleep apnea variables showed severe OSA, with a median apnea-hypopnea index of 42.7 events/h (IQR, 27.5–58.1) or a median oxygen desaturation index of 43.0 (IQR, 26.0–74.0). The median duration of CPAP therapy was 1.3 years (IQR, 0.4–2.9 years), with a minimum duration of 30 days. The CPAP adherence download showed a median nightly usage of 5.4 hours

Table 1—Participant characteristics.

	All (n = 108)	Low Adherence (< 4 h) (n = 24)	High Adherence (> 4 h) (n = 84)	*P*
Baseline characteristics				
Age (y)	56.0 (12.8)	55.4 (15.0)	56.5 (12.2)	.53
Male, n (%)	78 (72.2)	16 (67.0)	62 (74.0)	.49
BMI (kg/m^2)	37.7 (11.5)	33.2 (5.8)	39.1 (12.4)	.02
Charlson-Deyo comorbidity index, median (IQR)	2.0 (1.0–5.0)	4.0 (2.0–5.0)	2.0 (1.0–4.0)	.09
Heart failure, n (%)	27 (25.0)	8 (33.3)	19 (22.6)	.29
Chronic lung disease, n (%)	61 (56.5)	12 (50.0)	49 (58.3)	.47
Malignancy, n (%)*	15 (13.9)	3 (12.5)	12 (14.3)	.99
Baseline ESS score	9.8 (5.6)	11.4 (5.7)	9.4 (5.5)	.13
Baseline HADS-D score	6.5 (3.9)	6.8 (3.9)	6.4 (3.9)	.69
Baseline HADS-D ≥ 8, n (%)	40 (37.0)	10 (41.6)	30 (35.7)	.64
Baseline HADS-A score	7.2 (4.1)	7.9 (4.9)	7.0 (3.9)	.23
Baseline HADS-A ≥ 11, n (%)	19 (17.6)	6 (25.0)	13 (15.5)	.36
Sleep apnea characteristics				
Diagnostic polysomnography (53/108)				
AHI (events/h), median (IQR)	42.7 (27.5–58.1)	49.8 (27.6–70.0)	39.6 (26.1–56.3)	.27
Minimum oxygen saturation (%), median (IQR)	79.0 (69.0–84.0)	80.0 (70.0–85.0)	78.0 (69.0–84.0)	.51
Total sleep time (h), median (IQR)	6.1 (5.2–6.9)	5.9 (5.2–6.4)	6.1 (5.2–7.3)	.25
Sleep efficiency (%), median (IQR)	77.6 (65.7–85.7)	76.4 (61.0–83.6)	77.6 (68.0–86.7)	.44
Sleep latency (min), median (IQR)	11.0 (5.0–22.5)	9.8 (7.0–13.5)	11.0 (5.0–28.0)	.88
Proportion REM sleep (%), median (IQR)	10.4 (5.7–17.4)	10.3 (0.8–17.4)	10.4 (6.1–17.4)	.61
Diagnostic overnight oximetry (55/108)				
ODI (events/h), median (IQR)	43.0 (26.0–74.0)	33.0 (20.0–55.0)	48.0 (29.0–75.0)	.17
Minimum oxygen saturation (%), median (IQR)	80.0 (72.0–85.0)	81.0 (74.0–88.0)	80.0 (71.0–84.0)	.25
Time oxygen saturation < 88% (%), median (IQR)	1.0 (0.0–5.0)	1.0 (0.0–5.0)	1.0 (0.0–6.0)	.34
Mean heart rate, median (IQR)	72.0 (59.0–80.0)	67.5 (59.0–81.0)	75.0 (61.0–80.0)	.46
CPAP characteristics				
Duration of CPAP therapy (y), median (IQR)	1.3 (0.4–2.9)	1.7 (0.7–3.6)	1.3 (0.4–2.4)	.39
CPAP pressure (cm H_2O), median (IQR)	10.0 (9.0–12.0)	10.0 (9.0–12.0)	11.0 (10.0–13.0)	.54
CPAP nightly usage (h), median (IQR)	5.4 (4.1–7.3)	1.4 (1.1–3.2)	6.2 (5.2–7.8)	< .001
Days CPAP used > 4 h (%), median (IQR)	73.5 (31.1–90.0)	25.0 (16.0–43.0)	84.0 (69.3–93.0)	< .001
Nights CPAP used/90 d, median (IQR)	81.0 (48.0–89.0)	42.0 (28.0–57.0)	86.0 (73.0–90.0)	< .001
Duration of CPAP (y), median (IQR)	1.3 (0.4–2.9)	1.7 (0.7–3.6)	1.3 (0.4–2.4)	.39

Results displayed as mean (SD), unless otherwise indicated. *Malignancy means an active or past history of solid organ or blood malignancy. AHI = apnea-hypopnea index, BMI = body mass index, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, HADS = Hospital Anxiety and Depression Scale, HADS-A = Hospital Anxiety and Depression Scale–Anxiety, HADS-D = Hospital Anxiety and Depression Scale–Depression, IQR = interquartile range, ODI = oxygen desaturation index, REM = rapid eye movement, SD = standard deviation.

(IQR, 4.1–7.3 hours) with a minimal residual apnea-hypopnea index (1.8 events/h [IQR, 1.0–4.6 events/h]) and a low leak (1.0 L/min [IQR, 0.0–4.8 L/min]). We found that 12.0% of participants (13/108) self-reported symptoms of insomnia.

Psychiatric data

The proportion of depression cases as defined by HADS-D ≥ 8 at baseline was 37.0%. We found that 40.7% of patients reported an active or previous diagnosis of depression, and 37.9% were currently prescribed antidepressant or anxiolytic medication. Sleep physicians reported a depressive disorder in 21.3% of patients, as per review of the electronic medical record. At baseline there were no significant sex differences in the mean HADS-D of men and women (P = .16) or in the proportion of depression cases (P = .32). The proportion of anxiety cases at baseline was 17.6%

Table 2—Change in HADS and ESS score post-CPAP therapy.

	Baseline	Follow-up	Unadjusted			Adjusted		
			Mean Difference	95% CI	*P*	Estimated Mean Difference	95% CI	*P*
HADS-D score	6.5	5.3	–1.2	–2.0 to –0.5	.002	–1.4*	–2.1 to –0.6*	.001*
HADS-D ≥ 8, n (%)	40 (37.0)	30 (27.8)	–9.2	–19.7 to –1.2	.08	–10.7†	–21.4 to –0.1†	.05†
HADS-A score	7.2	6.0	–1.1	–1.8 to –0.4	.001	–1.1*	–1.8 to –0.35*	.004*
HADS-A ≥ 11, n (%)	19 (17.6)	17 (15.7)	–1.9	–8.6 to 5.0	.59	–1.7†	–8.7 to 5.3†	.63†
ESS score	9.8	7.0	–2.8	–3.8 to –1.8	< .001	–2.8*	–3.8 to –1.8*	< .001*

n = 108. Data presented as means. *Adjusted for baseline value, duration of CPAP, ESS score, and Charlson-Deyo comorbidity index. †Adjusted for baseline value and duration of CPAP. CI = confidence interval, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, HADS = Hospital Anxiety and Depression Scale, HADS-A = Hospital Anxiety and Depression Scale–Anxiety, HADS-D = Hospital Anxiety and Depression Scale–Depression.

Table 3—Change in HADS and ESS score between adherence groups.

	Low Adherence (< 4 h)			High Adherence (> 4 h)			Adherent vs Nonadherent			
							Unadjusted		Adjusted*	
	Baseline (n = 24)	Follow-up (n = 24)	Mean Difference	Baseline (n = 84)	Follow-up (n = 84)	Mean Difference	Mean Difference (95% CI)	*P*	Estimated Mean Difference (95% CI)	*P*
HADS-D score, mean (SD)	6.8 (3.9)	6.5 (4.1)	–0.3	6.4 (3.9)	4.9 (3.9)	–1.5	–1.3 (–3.1 to 0.5)	.16	–1.2 (–3.0 to 0.6)	.19
HADS-A score, mean (SD)	7.9 (4.9)	7.0 (4.2)	–0.9	7.0 (3.9)	5.8 (4.2)	–1.2	–0.2 (–1.9 to 1.4)	.79	–0.3 (–2.0 to 1.4)	.74
ESS score, mean (SD)	11.4 (5.7)	9.4 (4.5)	–2.0	9.4 (5.5)	6.3 (4.7)	–3.1	–1.1 (–3.4 to 1.3)	.38	–1.0 (–3.5 to 1.4)	.39

*Adjusted for baseline value and duration of CPAP. CI = confidence interval, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, HADS = Hospital Anxiety and Depression Scale, HADS-A = Hospital Anxiety and Depression Score–Anxiety, HADS-D = Hospital Anxiety and Depression Score–Depression, SD = standard deviation.

(HADS-A ≥ 11), 27.7% of patients reported a diagnosis of anxiety, and 8.3% had a physician-recorded diagnosis.

Primary outcome: change in HADS

Across all participants there was a statistically significant reduction in depression and anxiety subscales and ESS score at the time of follow-up, post-CPAP treatment. The mean reduction in HADS-D was –1.2 (95% confidence interval [CI], –2.0 to –0.5; *P* = .002), and the mean reduction in HADS-A was –1.1 (95% CI, –1.8 to –0.4; *P* = .001). The results were similar after adjustment for baseline value, duration of CPAP therapy, ESS score, and Charlson-Deyo comorbidity index (**Table 2**). The estimated mean reduction in HADS-D after adjusting for the above variables remained statistically significant at –1.4 (95% CI, –2.1 to –0.6; *P* = .001).

Secondary outcomes

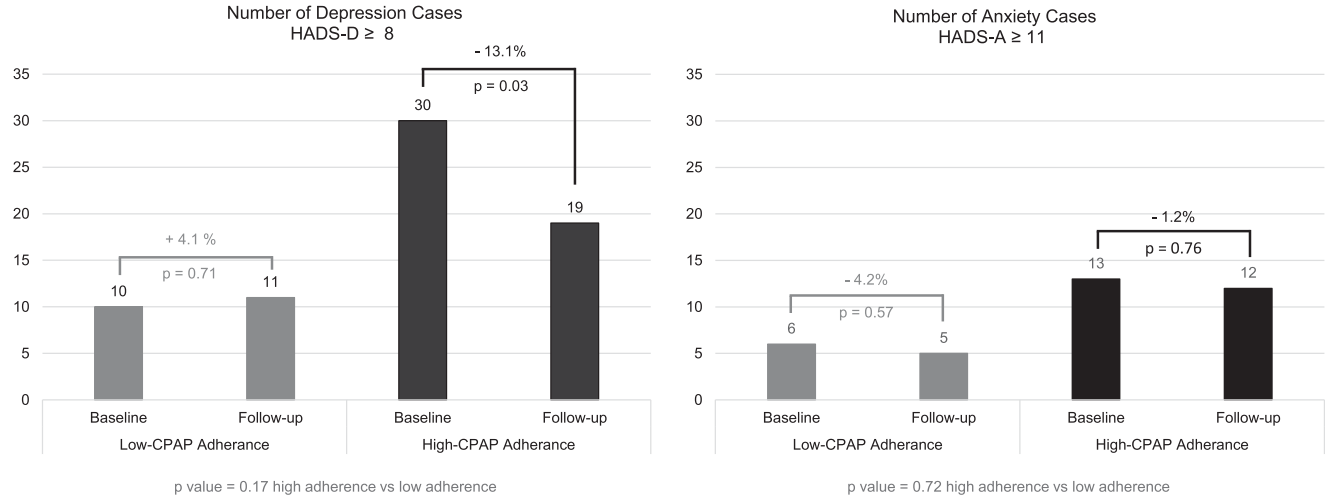
There was a statistically significant reduction in the number of depression cases (HADS ≥ 8) across all participants after CPAP therapy, with an estimated reduction of 10.7%, when adjusted for baseline value and duration of CPAP therapy (95% CI, –21.4% to –0.1%; *P* = .05). There was no significant change in the number of anxiety cases across all participants.

The mean reduction in HADS-D in those with high CPAP adherence (n = 84) was –1.5 and –0.3 in those with low CPAP adherence (n = 24). The high-CPAP-adherence group had a tendency toward a greater reduction in HADS-D, with an unadjusted difference of –1.3 (95% CI, –3.1 to 0.5; *P* = .16). This finding remained similar when adjusting for baseline value and duration of CPAP, with an adjusted estimated difference of –1.2 (95% CI, –3.0 to 0.6; *P* = .19) (**Table 3**).

There was no significant difference in the change in HADS-A between adherence groups, with a reduction of –1.2 in the high-CPAP-adherence group and –0.9 in the low-adherence group (adjusted estimated mean difference, –0.3; 95% CI, –2.0 to 1.4; *P* = .74).

In an unadjusted analysis, in participants with high CPAP adherence there was a 13.1% reduction in the number of depression cases after initiation of CPAP therapy (*P* = .03), compared to an increase of 4.1% in the low-CPAP-adherence group (*P* = .71), but there was no significant difference when comparing the groups (unadjusted difference, –17.3%; 95% CI, –42.2% to –7.6%; *P* = .17). There was no significant

Figure 2—Graph of absolute number of depression and anxiety cases per adherence group.



CPAP = continuous positive airway pressure, HADS-A = Hospital Anxiety and Depression Scale–Anxiety, HADS-D = Hospital Anxiety and Depression Scale–Depression.

change in the number of anxiety cases in either adherence group (**Figure 2**).

DISCUSSION

This study has shown a statistically significant reduction in depression scores after the initiation of CPAP treatment of –1.4 (adjusted 95% CI, –2.1 to –0.6; $P = .001$), which was clinically significant[35,36] in those with high CPAP adherence at –1.5. There was also a statistically significant reduction in the number of depression cases (ie, HADS ≥ 8) across all participants after CPAP therapy of –10.7% (adjusted 95% CI, –21.4 to –0.1; $P = .005$), with a trend toward a greater reduction in those with high CPAP adherence. However, the analyses comparing CPAP adherence groups were likely limited in statistical significance because of low numbers in the low-CPAP-adherence group.

Despite a statistically significant reduction in HADS-A across all participants in our study, there was no significant reduction in HADS-A between adherence groups or in the number of anxiety cases. Multiple other studies have also not shown a significant change in anxiety after OSA treatment.[11,14]

There has been significant uncertainty in the previously published literature examining depression scores after CPAP therapy. Some studies have shown a significant reduction in depression scores,[10,12,40,41] whereas others have not[15,16] or have been inconclusive.[13,14] The most recently published meta-analysis of mood scores post-CPAP, by Zheng et al,[11] found an overall reduction in depressive symptoms with CPAP with a standardized mean difference of –0.18 but no effect of CPAP treatment when compared to sham CPAP. Furthermore, there are several limitations of the trials included in this meta-analysis. Of the 17 studies included, 12 studies had a follow-up duration of ≤1 month,[17–28] 11 studies had ≤50 participants,[17–20,22–27,29] and change in mood scores was a secondary analysis rather than a primary endpoint in 13 of the 17 studies included.[10,16,20,22–31] In addition, some of these studies used a depression scale not specifically validated in the sleep clinic setting. Our study adds to the existing literature by providing real-world evidence that CPAP therapy in specialized sleep clinics does in fact reduce depression scores in patients with OSA.

The strengths of our study include the longer duration of follow-up and that it is representative of a real-world effect, rather than in a controlled clinical trial environment, making it generalizable and applicable to the sleep clinic setting. Our study was performed using a robust screening tool for mood disorders, the HADS, which has been previously validated specifically in the sleep clinic population. This element is of utmost importance given the overlapping symptoms that OSA and depression share. In our study, the follow-up duration varied because of the study design, although the median duration of CPAP therapy was 1.3 years, as compared to 30–90 days in the majority of other studies.[11,13]

Secondary endpoints of several large, randomized controlled trials in OSA have also suggested a reduction in depression scores with CPAP therapy. The Sleep Apnea Cardiovascular Endpoints study,[10] the largest randomized controlled trial in OSA to date, randomized 2,717 adults, a predominantly non-sleepy Asian population, with moderate-severe OSA to CPAP or usual care. The study showed a reduction in HADS-D of –0.8 ± 4.0 with CPAP compared to –0.1 ± 3.8 in the control group ($P < .001$). The larger reduction in HADS-D seen in our study may be because our study included sleepy patients with comorbid depression, whereas other studies excluded patients with high ESS scores, significant comorbidities, or behavioral disorders.

A subsequently published secondary analysis of the Sleep Apnea Cardiovascular Endpoints study showed no significant effect of CPAP treatment on anxiety cases but a statistically significant reduction in depression cases. The odds ratio for reduction in patients with clinically significant depression (HADS > 8) was calculated at 0.80 ($P = .031$), with a

number needed to treat of 15 to prevent 1 case of depression.[11] This finding is similar to the effect size on depressive symptoms seen with 12 weeks of sertraline use in patients in the primary care setting.[42,43]

Similarly, a secondary analysis from the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea trial found that in nonsleepy patients with OSA and coronary artery disease, 56 participants with an elevated Zung Self-Rating Depression Scale at baseline had improvement in depression scores after 3 months of CPAP treatment, which persisted at 12 months compared to the no-CPAP group (P = .01).[12] The study showed that the proportion of patients with significant depressive symptoms (Zung Self-Rating Depression Scale > 50) decreased from 30% at baseline to 13% at 12 months in those randomized to CPAP, as compared to 25% at baseline and 24% at 12 months in the no-CPAP group.[12] This finding is similar to the results of our study, which showed that in those with high CPAP adherence the proportion of depression cases decreased from 35.7% at baseline to 22.6% post-CPAP therapy.

Results from other studies further support the reduction in depression scores seen in our study. Edwards et al[40] conducted a prospective cohort study that showed a reduction in a Patient Health Questionnaire-9 score from 11.3 to 3.7 after 3 months of CPAP therapy in patients with CPAP adherence of more than 5 hours per night. Edwards et al showed that 18.3% of patients reported thoughts of suicidality or self-harm at baseline, compared with 0% of patients post-CPAP treatment, although their findings were limited by the short follow-up period.

The results of our study showed high rates of depression and anxiety cases, of 40% and 19% respectively, in those with OSA as measured by the HADS at baseline. We found that 38% of patients were actively prescribed an antidepressant or anxiolytic medication. This finding is consistent with other studies, with a recent large pooled meta-analysis estimating that 23% of patient with OSA have clinical depression.[4] The difference between patient- and physician-reported prevalence in this study highlights the ongoing need for clinicians to discuss mental health and patients' perception of mood disorders.

This study was not designed to show causation. As such, there are several confounders, which could also contribute to the reduction in depression scores in addition to CPAP therapy. It is likely that other aspects of patient care could also result in a reduction of depression scores, including contact with health professionals in attending a sleep clinic, undergoing thorough clinical assessment with potential referral to other services, and broader specialized care. We could not measure or control for the influence of concurrent lifestyle and healthy sleep advice in this study. Other limitations included that in some patients with a high pretest probability for OSA, pulse oximetry was used for the diagnosis of OSA, as per the discretion of the experienced sleep physician. CPAP adherence download for the proceeding 90 days may also not be representative of participants' long-term usage. The statistical and clinically significant[44] reduction in the ESS score across participants may also confound the reduction in depression scores. However, the mean reduction in HADS-D remained similar and statistically significant after adjusting for the baseline ESS score in addition to the Charlson-Deyo comorbidity index, baseline value, and duration of CPAP.

Several factors may also reduce the effect on the depression scores seen. Selection bias may contribute because only those patients motivated to attend the follow-up clinic were recruited, and as such patients with very well-controlled OSA and who were stable on CPAP were likely underrepresented because of infrequent clinic follow-up or discharge from the sleep clinic. Given the high rates of medical comorbidities in this group, deteriorating health and its psychological consequences may also reduce the effect size seen over time; in our study, the median follow-up period was 1.3 years to a maximum of 5.4 years.

OSA and depression are common, often coexistent disorders that share a multidirectional relationship. Multiple psychopathophysiological mechanisms have been proposed in the literature to date. It is possible that OSA may contribute to worsening depression via sleep loss, sleep disruption, intermittent hypoxemia, neurotransmitter imbalance, and proinflammatory cytokine imbalance.[41,45,46] Other studies have suggested that the intermittent hypoxia of OSA may result in direct neuronal damage visible on neuroimaging, resulting in a reduction in neurocognitive performance.[46–48] These effects may be reversible with CPAP therapy.[47] Furthermore, depression may worsen OSA via psychoactive and antidepressant medication usage, sleep disruption, circadian imbalance, and reduced adherence.[41,45,49] The effects of weight gain and metabolic syndrome may also contribute to the worsening of both disorders. Treatment resistance in depression has been linked with OSA,[8] and similarly, treatment-resistant OSA been linked to depression.[9] Further work teasing out this complex psychopathophysiological mechanism is needed.

Several unanswered questions remain regarding depression and OSA treatment in the current literature. The HADS and the many other screening tools for depression are not diagnostic of major depressive disorder. As such, further work is needed regarding the effect of CPAP on major depressive disorder or on treatment-resistant depression. Ultimately, a randomized controlled trial in patients with coexistent depression and OSA is required.

This study shows that OSA treatment with CPAP improves depression scores. Many clinical implications arise from this finding, including patient education regarding potential improvement in mood and rates of depression, which could help motivate patient adherence. In addition, with these findings, perhaps there should be a lower threshold to refer patients to specialized sleep clinics or to initiate CPAP in those patients with coexistent depressive symptoms.

CONCLUSIONS

Depression is very common in patients with OSA. Depression is difficult to treat, requiring a multifaceted approach. CPAP in specialized sleep clinics improves depression scores. Therefore, sleep apnea treatment is a modifiable factor that may have a significant effect on the burden of disease that depression produces in our community.

ABBREVIATIONS

CI, confidence interval
CPAP, continuous positive airway pressure
ESS, Epworth Sleepiness Scale
HADS, Hospital Anxiety and Depression Scale
HADS-A, Hospital Anxiety and Depression Scale–Anxiety
HADS-D, Hospital Anxiety and Depression Scale–Depression
IQR, interquartile range
OSA, obstructive sleep apnea

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