

SCIENTIFIC INVESTIGATIONS

For Individuals with Obstructive Sleep Apnea, Institution of CPAP therapy is Associated with an Amelioration of Symptoms of Depression which is Sustained Long Term

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Objective: To assess the sustainability of an improvement in symptoms of depression using CPAP therapy in patients with obstructive sleep apnea.

Patients/Methods: Patients referred to our center for evaluation of obstructive sleep apnea who had a respiratory disturbance index (RDI) of ≥ 15 and who demonstrated a significant response to CPAP (50% or greater drop in RDI), were evaluated for symptoms of depression using the Beck Depression Inventory-Fast Screen for Medical Patients (BDI). These individuals were asked to complete the BDI assessment again after 4 to 6 weeks of treatment with CPAP (short-term follow-up), and then reassessed approximately one year later (long-term follow-up).

Results: In this group of patients, the institution of CPAP therapy resulted

in a significant decrease in those symptoms of depression assessed by the BDI at both the short-term and long-term follow-up periods.

Conclusions: For patients with OSA who continue CPAP therapy, we noted a statistically significant, sustained improvement in those symptoms of depression measured by the BDI.

Keywords: Sleep, obstructive sleep apnea, CPAP, depression

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INTRODUCTION

We noted that a substantive number of the individuals referred to our center for evaluation of possible obstructive sleep apnea (OSA) had been prescribed antidepressant medications prior to referral. When evaluated with the Beck Depression Inventory- Fast Screen for Medical Patients (BDI),¹ we found that 41% of our patients had a score suggesting at least mild symptoms of depression, and 12% had a score suggesting moderate to severe symptoms of depression. The prevalence, in our patients, of symptoms suggesting the diagnosis of depression, and the incidence (39%) of having been prescribed antidepressant medication prior to referral for a suspected diagnosis of OSA, seemed disproportionate to the incidence of depression in the general population.²⁻⁴ Therefore, we speculated that the fatigue and sleepiness with which individuals with OSA may suffer, might be misinterpreted as symptoms of depression, or that adverse effects of OSA might affect the expression of clinical depression. Though the specific mechanism of the association of symptoms of depression with OSA remains undefined, we wondered whether, in patients with the obstructive sleep apnea syndrome (OSAS), these symp-

toms might be amenable to treatment with continuous positive airway pressure (CPAP).

In our initial report on the effect of CPAP therapy⁵ we noted a statistically significant improvement in those symptoms of depression defined by the BDI at the time of the patient's first follow-up appointment which was scheduled 4 to 6 weeks after they had begun CPAP therapy at home. Whether the improvement would be sustained with ongoing treatment was unknown. To further assess this question we reevaluated patients at the time of long-term follow-up, typically one year or more after CPAP had been initiated.

METHODS

Subjects

All patients referred for evaluation of the OSAS were eligible for entry into the study. Each was interviewed and examined by a board certified sleep specialist, and found to meet standard indications for polysomnographic evaluation for the suspected diagnosis of OSA.⁶

Individuals with a baseline RDI ≥ 15 who demonstrated a 50% or greater decrease in the RDI with CPAP were eligible for the study. We chose an RDI ≥ 15 in an effort to establish a defined group with moderate to severe OSA, and insisted upon a minimum of a 50% improvement in order to define a group with a disorder clearly amenable to CPAP. CPAP was titrated by protocol with the goal to reduce the RDI to < 5 if possible. The optimal CPAP pressure was chosen after review by the board certified sleep specialist.

All patients were asked to complete an Epworth Sleepiness Scale (ESS)⁷ and the Beck Depression Inventory- Fast Screen for Medical Patients (BDI)¹ at the time of their initial assessment

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(before any testing or treatment) and again at the time of their follow-up appointment after having used CPAP at home for 4 to 6 weeks. Those individuals attesting to the nightly use of CPAP (≥ 6 hours/night, 7 nights/week), are included in this report. Any individual who indicated that use of CPAP was sporadic or was < 6 hours/night was excluded from the study.

Those individuals who initially reported success in using CPAP at the time of their first reevaluation were asked to complete these same forms at the time of our attempted long-term follow-up. We had asked that they return for follow-up to the center, but many did not. Those who did not were contacted by letter encouraging them to contact us and asking them to complete the forms (we provided a stamped, self-addressed return envelope). Follow-up data was limited to those willing to respond; this report details the findings for the first 50 consecutive individuals who did.

Eleven patients who responded to our request for long-term follow-up were excluded from this analysis. Seven patients were excluded because they attested to using CPAP intermittently or < 6 hours per night (these patients were re-contacted and asked to return to the center to assess the nature of the problem which was limiting their use of CPAP); 4 patients were excluded because they had undergone surgery for OSA and were no longer using CPAP.

This study was reviewed and approved by the Research Ethics Review Board of University Community Hospital.

The Epworth Sleepiness Scale (ESS)

The Epworth Scale^{7,8} asks the individual to rate the likelihood of dozing in 8 specific situations, answered on a scale of 0-3, zero being little or no chance of dozing, and 3 representing a high chance of dozing. Therefore the scale goes from 0-24. There is no fixed scoring recommendation but a score of ≥ 10 is probably abnormal, and a score > 14 might suggest a more significant degree of daytime hypersomnolence.^{9,10}

The Beck Depression Inventory - Fast Screen for Medical Patients (BDI)

This tool¹ asks 7 questions pertaining to feelings of sadness, discouragement about the future (Pessimism), personal failures, perceived decreases in self-confidence, a sense of being overly self-critical, the ability to derive pleasure from things (Anhedonism), and suicidal ideation. It is perhaps important to point out that none of the questions on the BDI ask about fatigue, tiredness, sleepiness, or any of the more traditional symptoms usually attributable to the OSAS.

Each question on the BDI is answered on a scale of 0-3 (zero being little or none, and 3 representing a high level of the characteristic in question). Therefore the scale for the sum of the 7 questions goes from 0-21. The suggested scoring¹ is 0-3 = minimal symptoms of depression, 4-6 = mild symptoms of depression, 7-9 = moderate symptoms of depression, and 10-21 = severe symptoms of depression.

Polysomnography

A standard PSG in our lab uses the following protocol: After the patient is acclimated to the facility, they are fitted with electroencephalographic (C3/A2,C4/A1,O2/A1,O1/A2), electrooculographic (ROC/A1,LOC/A2), and electromyographic (chin EMG)

electrodes for sleep staging, according to the criteria outlined by Rechtschaffen and Kales.¹¹ Electrodes are placed on both legs, as described in ASDA Atlas Task Force Report, to monitor myoclonic activity.¹² Uncalibrated inductive plethysmography bands are used to monitor chest and abdominal movement, and impedance devices are placed to monitor intercostal muscle activity. A nasal pressure transducer (Pro-Tech, WA) is used to monitor airflow. Pulse oximetry (Nonin, MN) is assessed at the finger to evaluate oxygen saturation. Electrocardiographic leads are placed to monitor cardiac rhythm (modified lead 2). Concurrent monitoring of audio, video, and body position, supplement the other measured parameters.

Definition of PSG Scoring Parameters

Sleep staging was scored according to the criteria of Rechtschaffen and Kales.¹² Arousals were scored as defined in the ASDA Atlas Task Force Report on EEG Arousals.¹³ Respiratory events were scored as follows: An apnea was defined as a reduction of the measured parameter of airflow to 10% of baseline or less, with a duration ≥ 10 seconds. A hypopnea was defined as any reduction of the measured parameter of airflow with a duration ≥ 10 seconds, which was accompanied by $\geq 4\%$ decrease in measured oxygen saturation, or a contiguous arousal. The respiratory disturbance index (RDI) was defined as the total number of apneas and hypopneas / hour of sleep.

Statistical Analysis

These data were analyzed using SPSS version 12.0 (SPSS Corporation, Chicago, IL). Data presented are mean \pm one standard deviation. A paired samples t-test was used for scalar data, and the Wilcoxon signed ranks test or Mann Whitney test was used for ordinal data as indicated.

RESULTS

Demographics

This report delineates the data for the first 50 consecutive individuals who responded to our long term follow-up request (39 of the 50, or 78% were males). The average time to long term follow-up was 600 ± 239 days. The average age of these individuals was 53 ± 11.3 years; their average body mass index was 35 ± 7.7 .

These 50 patients represent 45% of the eligible respondents. There were 61 "nonrespondents" (individuals who failed to respond to our request for long-term follow-up despite attempts by mail and by phone). Of these 61, 43 (70%) were males, with an average age of 48.7 ± 10.4 , and a body mass index of 36.3 ± 9.1 (not significantly different from the study group).

Polysomnographic Data

The polysomnographic data for the study group (RDI 57.4 ± 31.1 at baseline and 5.2 ± 4.2 with CPAP) confirms that these individuals had severe OSA and demonstrated a significant improvement with CPAP.

The 61 nonrespondents had an RDI of 59.4 ± 36.5 at baseline and 5.1 ± 5.4 with CPAP (no significant difference when compared to the study group).

Table 1—BDI Before and after CPAP (Mean +/- One SD)

	Number of Individuals	BDI Baseline	BDI at Initial F/U on CPAP	p Baseline vs Initial F/U	BDI at Long Term F/U on CPAP	p Baseline vs Long Term F/U	p Initial F/U vs Long Term F/U
Initial BDI- (0-21)	50	2.4 ± 3.0	0.5 ± 1.0	<0.0001	0.6 ± 1.5	<0.0001	0.642
Initial BDI >0 (1-21)	32	3.8 ± 3.0	0.7 ± 1.2	<0.0001	0.9 ± 1.8	<0.0001	0.896
Initial BDI >3 (4-21)	15	6.1 ±2.9	1.2 ±1.6	0.001	1.3 ±2.1	0.001	0.773
Initial BDI >6 (7-21)	5	9.4 ± 2.8	2.4 ± 2.1	0.042	2.4 ± 3.1	0.068	1.00

Wilcoxon signed ranks test

Antidepressant Medication Use

Nine of the 50 study group patients (18%) had been on an antidepressant medication at the time of the initial referral and each was on a stable dose of their antidepressant medication ≥ 2 months prior to their initial evaluation. At the time of long-term follow-up, 3 of these 9 had discontinued their antidepressant medication. Of the 41 patients who had not been on an antidepressant medication at the time of their initial evaluation, none had been started on one when assessed at the time of their long-term follow-up.

Twenty-two of the 61 nonrespondents (36%) had been prescribed an antidepressant prior to their initial referral (this is significantly higher than the study group, $p < 0.001$).

Analysis of Pre-CPAP and Post-CPAP changes in BDI

At the initial follow-up, having used CPAP at home consistently for 4 to 6 weeks, the BDI demonstrated a significant decrease (Table 1). Eighteen of the 50 subjects had an initial BDI score of zero. Two of these individuals demonstrated an increase from zero to one on the initial follow-up BDI, the rest remained at zero.

Of those patients for whom a decrease in the BDI was possible (initial BDI >0), 94% (30/32) were found to have experienced a fall in the BDI. The other two patients were unchanged (one stayed at a BDI of one, and the other stayed at a BDI of two). Of those patients who had an abnormal BDI (>3) before CPAP, 100% (15/15) were noted to have had a fall in the BDI at the time of the initial follow-up, and the average decrease was 4.9 (from an initial value of 6.1 to a value of 1.2 after CPAP).

What these data also demonstrate (Table 1) is that the decline in BDI noted at the time of the initial follow-up was maintained long term. A statistically significant change from the baseline is sustained at the time of long term follow-up, and no difference is identified between the values for the initial follow-up and the long-term follow-up BDI scores. These findings are consistent for the group as a whole (44/50 or 88% sustaining the improved BDI scores), for those who began with a BDI > zero (28/32 or 88% sustaining the improved BDI scores), and for those who began with an elevated baseline BDI, defined as >3 (14/15 or 93% sustaining the improved scores).

Of the 6 individuals who failed to demonstrate a sustained de-

crease in the BDI, 3 were unchanged starting at 1, 1, and 7 respectively, and 3 increased (0 to 1, 0 to 2, and 2 to 6).

Segregating these data into those who had or had not been prescribed antidepressant medication prior to referral (Table 2), it was noted that although the patients for whom an antidepressant had been prescribed had a higher initial BDI than those for whom one had not been prescribed, both groups showed a decrease in BDI after CPAP, which was sustained long term (the group for whom antidepressants had been prescribed failed to meet a p value of <0.05, perhaps because of the small size of this group).

The 61 nonrespondents had a higher initial BDI than the 50 respondents (3.9 ± 4.9 vs. 2.4 ± 3.0 , $p = 0.007$) though at the time of their 6-week follow-up visit, the BDI for the nonrespondents had decreased to 0.8 ± 1.5 , which was not significantly different from the study group whose BDI had decreased to 0.5 ± 1.0 ($p = 0.488$). Of the 61 nonrespondents, 39 had not been prescribed an antidepressant at the time of their initial presentation; for these 39 individuals the initial BDI was 3.5 ± 3.1 and decreased to 0.5 ± 1.2 at the time of their first follow-up ($p < 0.0001$). Twenty-two of the 61 had been prescribed an antidepressant; for these 22 individuals the initial BDI was 4.6 ± 4.1 and decreased to 1.3 ± 2.0 at the time of their initial follow-up ($p < 0.0001$). By definition, we have no data on long-term follow-up for these 61 individuals.

Table 2—BDI delineated by Prior Prescription of an Antidepressant Medication (Mean \pm One SD)

	Not Prescribed Antidepressants (n = 41)	Prescribed Antidepressants (n = 9)	p
BDI Baseline	2.1 \pm 2.7	4.2 \pm 3.7	0.084
BDI Initial CPAP	0.3 \pm 0.6	1.4 \pm 1.9	0.026
p Baseline vs Initial CPAP	<0.0001	0.018	
BDI Long Term CPAP	0.3 \pm 0.6	2.1 \pm 2.8	0.057
p Baseline vs Long Term CPAP	<0.0001	0.149	
p Initial CPAP vs Long Term CPAP	1.00	0.457	

Analysis between groups – Mann Whitney test

Analysis of change within a group – Wilcoxon signed ranks test

The Epworth Sleepiness Scale for the primary study group improved from a baseline of 13.8 ± 4.9 before CPAP, falling to 6.0 ± 3.7 after CPAP initially, and was sustained at the time of long-term follow-up at 5.7 ± 3.4 ($p < 0.0001$). Whether the improvement in the patients' perceived sleepiness may have had an effect on the BDI responses cannot be determined on the basis of this study, but this possibility should be acknowledged.

DISCUSSION

We and others have documented the association between some symptoms of depression and OSA,^{5,14,15,16} noting that patients with the OSAS will frequently report feeling tired, fatigued, sleepy, and poorly motivated.^{17,18} They may have difficulty concentrating or remembering factual data, they may become irritable or withdrawn, and they may find themselves losing interest in, or deriving little pleasure from activities which should be an integral part of their lives.¹⁹⁻²¹ These consequences of OSA may affect the individual's ability to perform their job, can undermine a relationship with their family, and may ultimately limit their ability to enjoy life.²²⁻²⁴ This may result in their presenting to the physician with symptoms which might be ascribed to depression, and may potentially even fulfill the criteria for a major depressive episode using DSM IV criteria.²⁵

Whether the diagnostic problem is that the presenting symptoms in both syndromes (OSA and depression) are similar enough to result in the potential for the practitioner to confuse one with the other, leading to a misdiagnosis, or whether one disorder might increase the likelihood of the other occurring, is unknown.

Previous studies have documented improvement in some symptoms of depression in patients with OSA after institution of CPAP therapy. However, most of these reports, including our own, have been limited to relatively short-term follow-up (4-12 weeks).

One exception in this regard is the report by Sin et al²⁶ who present data for a one-year follow-up, but they used a more general tool aimed at assessing overall well-being. They noted that, in their group of patients with OSA, the Overall Emotional Summary scores, and the Vitality scores (as defined from the Medical Outcomes Study Short Form, SF-36), were improved by CPAP and this improvement was sustained at the one-year follow-up. This study by Sin et al did not address specific symptoms of depression.

A study reported by Borak et al²⁷ failed to identify any improvement in emotional status after one year of treatment, but their data was limited to 16 patients and thus may not have had adequate power to identify a difference if one existed. The only other long-term follow-up study we could identify in the literature is the report of Platon et al²⁸ which suggested the possibility of some improvement at 11-14 months follow-up, but this was limited to 5 patients. To the best of our knowledge, ours is the first report to provide specific details on the long-term follow-up of symptoms of depression in a large group of patients with well-documented OSA treated with CPAP.

Our study provides a distinct data base in which a group of individuals with a well defined syndrome, documented reversibility, and affirmed use of CPAP, have been followed and reassessed with a quantifiable measure of some symptoms of depression. Our data support the potential for CPAP use to be associated with an improvement in some measured symptoms of depression both in the short term (4-6 weeks) and long term (one year and longer).

There are any number of questions and criticisms which might

be appropriate when analyzing these data, not the least of which is the potential for inadvertent selection bias. We were not able to obtain long term follow-up data on all of our patients. This occurred for a variety of reasons. Ours is an area in which individuals will winter, then return north for the rest of the year. Upon their return to Florida, individuals may not be at the same address, and may not have the same phone number. In addition, most of our patients are members of health maintenance organizations which regulate access to specialists. If they report to their primary care physicians that they are doing well, they may not be granted access to a specialist for follow-up (even if we offer to see the individual at no charge, patients are frequently reluctant to be seen without a referral). Why these same individuals, or any individuals, might be reluctant to complete a form and return it in a self-addressed, stamped envelope, is perhaps more difficult to understand, but such was the case for a number of the individuals we contacted.

Thus, the lack of follow-up data for these 61 nonrespondents is a potentially significant factor, particularly as we note that these individuals had a higher incidence of having been prescribed an antidepressant prior to evaluation, and had a higher initial BDI. The improvement in the BDI in response to CPAP use at the time of their initial follow-up was equivalent to that seen in the study group, but whether the response would have been sustained long term is unknown. Whether these individuals failed to respond to our request for long-term follow-up because they were doing less well, or for some other reason, is likewise unknown, and thus the applicability of the findings of this study across a broader population may be in question. However, the inability to define the potential sustainability of any improvement which occurred for this group should not detract from the primary findings of this study which document a statistically significant improvement in those symptoms defined by the BDI for those patients who did follow up long term.

Another concern is that, as with our previous study, we did not monitor actual CPAP use (we did not have access to computerized internal monitors for each user), therefore the attestations of CPAP use might be inaccurate. We would suggest that even if inaccurate, the results of our study would likely be unchanged because it is unlikely for an individual to underestimate personal CPAP use (that is, it is very unlikely that someone would tell the physician that he or she was using CPAP for fewer hours/night than their actual use). It is possible, perhaps even likely, that some individuals overestimated their CPAP use (telling the physician that they used CPAP more hours/night than they actually did). If so, it would make the findings of this study even more significant, suggesting that CPAP use of fewer hours/night than the minimum upon which we insisted, might cause a similar improvement in the symptoms of depression we measured.

Yet another caveat is that the BDI scale we used assesses but a limited number of questions and fails to evaluate the full spectrum of symptoms with which depression may present. Nonetheless, it does ask questions about symptoms which might otherwise not have been typically associated with OSA by the clinician. Thus in asking specifically about sadness, pessimism, perceived personal failure, self-confidence, self-criticism, anhedonism, and suicidal ideation (with no mention of tiredness, fatigue, or sleepiness), it assesses symptoms which might not have been otherwise addressed.

As stated previously, our primary goal in this study was to evaluate, in a group of individuals with well-defined OSA and

ongoing use of CPAP therapy, whether changes in those symptoms of depression defined by the BDI would be sustained long term. These data support the conclusion that, in this group of individuals, long term CPAP use is associated with a statistically significant improvement in a measure of these symptoms.

Why the use of CPAP is associated with the changes in these symptoms is incompletely understood. Whether relief of the obstructive respiratory events with CPAP might ameliorate the symptoms by improving sleep continuity, by ameliorating the adverse effects of various neurotransmitters (catecholamines or cortisol-related peptides),^{29,30} by alleviating the adverse effects of any attendant hypoxemia,³¹ or by a mechanism as yet unknown, cannot be determined on the basis of the findings of our study; but the data from our study suggests that successful CPAP therapy is associated with a statistically significant improvement in those symptoms of depression delineated in the BDI, and that the improvement is sustained long term.

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