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The contribution of fatigue and sleepiness to depression in patients
attending the sleep laboratory for evaluation of Obstructive Sleep Apnea

Melinda L. Jackson* ^{1,2}; Con Stough ²; Mark E. Howard ³; Jo Spong³; Luke A.
Downey ²; Bruce Thompson⁴

¹ Sleep & Performance Research Center, Washington State University, Spokane, WA,
USA.

² Brain Sciences Institute, Swinburne University of Technology, Melbourne, Australia.

³ Institute for Breathing and Sleep, Austin Health, Melbourne, Australia.

⁴ Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital
and Monash University, Melbourne, Australia.

*To whom correspondence should be addressed

Dr Melinda Jackson

Sleep & Performance Research Center

Washington State University

Spokane, WA

United States of America, 99210

Phone: + 1 509 358 5576

Fax: + 1 509 358 7810

Email: jacksonm@wsu.edu

ABSTRACT

Purpose: A high prevalence of depressive symptomatology has been reported amongst sufferers of Obstructive Sleep Apnea (OSA), but it remains unclear as to whether this is due to their OSA or other factors associated with the disorder. The current study aimed to assess the incidence and aetiology of depression in a community sample of individuals presenting to the sleep laboratory for diagnostic assessment of OSA.

Methods: Forty-five consecutive individuals who presented to the sleep laboratory were recruited; of those, 34 were diagnosed with OSA and eleven were primary snorers with no clinical or laboratory features of OSA. Nineteen control subjects were also recruited. Patients and controls completed the Beck Depression Inventory (BDI), the Profile of Mood States (POMS), and the Epworth Sleepiness Scale (ESS) to assess their mood and sleepiness, prior to their polysomnography.

Results: All patients reported significantly more depressive symptoms compared to healthy controls, regardless of their degree of OSA. There were no significant differences between OSA patients and primary snorers on any of the mood and self-rated sleepiness measures. Depression scores were not significantly associated with any of the nocturnal variables. Regression analysis revealed that the POMS fatigue subscale explained the majority of the variance in subjects' depression scores.

Conclusions: Fatigue was the primary predictor of the level of depressive symptoms in patients who attended the sleep laboratory, regardless of the level of severity of sleep-disordered breathing. When considering treatment options, practitioners should be aware of the concomitant occurrence of depressive symptoms and fatigue in patients presenting with sleep complaints, which may not be due to a sleep disorder.

Key words: Obstructive Sleep Apnea, depression, fatigue, excessive somnolence disorder, primary snoring

Introduction

Depressive symptoms are commonly reported by patients with Obstructive Sleep Apnea (OSA), and higher rates of depressive symptomatology in OSA patients have been observed in a number of prevalence studies when compared to the general population [1-5]. Between 15% and 56% of OSA patients are diagnosed with a depressive disorder [2, 6-8] compared to only 6.6% of the general population[9]. The high prevalence of OSA (between 2% and 4% of the adult population [10]) and depression in the general population highlights the need for a clearer understanding of the association between these two conditions, both of which have a substantial economic and social public health burden [11-12].

Currently, there is conflicting evidence as to the exact relationship between OSA and depression [3, 13]. Some studies report an increase in depression score with increasing severity of OSA, pointing to the possibility of a causal relationship[3, 14]. The generalisability of the findings of these studies are somewhat limited due to their focus on patients with severe OSA, and the fact that they have included individuals taking antidepressant medication. Conversely, others have found no such relationship between disease severity and depressive symptoms in mild to moderate OSA patients [13, 15-16], and primary snorers [15]. This suggests that depressive symptoms may not be directly associated with nocturnal factors, but may also occur in those with milder forms of OSA, and thus other psychosomatic factors may contribute to the experience of depression.

Individuals who visit sleep laboratories generally complain of excessive daytime somnolence (EDS), fatigue [17-18] and neurocognitive dysfunction [2, 19-21]; symptoms which are also hallmarks of depression[22]. A number of Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV) criteria for Major Depressive Episodes are also features of the OSA sequelae, such as “fatigue” and “a diminished ability to think or concentrate” [22]. As such, it is difficult to determine whether a causal relationship exists between OSA and depression, or that the association exists due to conceptual overlap or a misinterpretation of the concepts of fatigue and sleepiness. A number of definitions have been postulated for both. There are distinct differences in the aetiology and outcomes of fatigue and sleepiness. Fatigue is a

gradual and cumulative process caused by sustained activity, and usually manifests as more of a physical state of exhaustion, which overlaps with other constructs, such as lethargy, lack of energy, tiredness, decreased strength, and difficulty with concentration[17, 23]. Sleepiness, on the other hand, is more often used to describe a subjective experience or feeling of difficulty remaining awake, or through objective measurement demonstrating increased sleep propensity [24]. The misconception of fatigue and sleepiness in patients attending sleep laboratories may contribute to measurement errors, and lead to people with depression presenting for evaluation for sleep disorders [4]. An indirect association between OSA and depression has been observed in previous studies, mediated by daytime sleepiness [13], or fatigue [17-18; 25], independent of disease severity. It is unknown whether subjective reports of sleepiness or fatigue are more responsible for the levels of depression in all patients who attend sleep laboratories.

The primary aim of this study was to investigate the degree of depression in a cross-sectional cohort of consecutive patients who present to the sleep laboratory, with different OSA severities compared to a group of healthy controls. This study also aimed to determine specific nocturnal and diurnal factors which may contribute to depressive symptomatology in these patients

Materials and Methods

Forty-five consecutive patients aged between 20 and 69 years (Mean age \pm SD = 49.56 ± 11.95 years) who presented to the sleep laboratory for a diagnostic sleep study and who satisfied the inclusion criteria were recruited. All patients had been referred to the laboratory for diagnostic assessment of OSA, and underwent an overnight polysomnography (PSG; Compumedics S-series, Compumedics Ltd, Melbourne Australia). After the PSG, participants were classified into two groups based on AASM criteria and previous studies: 1) OSA group (RDI $>$ 5); and 2) primary snorers (RDI $<$ 5)[26-27]. Nineteen age-matched controls (Mean \pm SD = 48.11 ± 9.31 years) were also recruited from a similar community population to the patient group. Patients and controls were excluded if they had a history of any neurological or psychiatric disorders, had a severe or unstable medical condition in

the preceding two months, regularly used medication that could adversely affect cognitive functioning, or were from a non-English speaking background. Control participants were also excluded if they had an Epworth Sleepiness Scale (ESS) score greater than 11 [28], or current or previous diagnosis of a sleep disorder, based on an overnight PSG and questionnaire. The study was approved by Swinburne University of Technology and Mitcham Private Hospital's Human Research Ethics Committees, and informed consent was obtained from all participants.

All participants completed a measure of current level of depression and mood prior to their diagnostic sleep study. Testing was performed by a trained research assistant. The Beck Depression Inventory (BDI-II) is a 21-item self-report inventory for assessing current levels of depression [29]. It is based on a series of key aspects of behaviour and emotion in which the respondent rates items on a four-point scale (0-3) with a potential range of total scores from 0 to 63. The BDI-II has previously been utilised to assess levels of depression in OSA patients [3-4, 30-31], and is used in this study to provide an empirical measure of the levels of depression in both patient groups and controls. The Profile of Mood States (POMS) is a well-established measure of mood disorder [32]. The POMS questionnaire consists of a 65-item, five-point adjective rating scale that reflects six primary mood factors: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, confusion-bewilderment and vigour-activity. The POMS was utilised in this study to identify whether mood state differences existed between patients and controls who attended a sleep laboratory, and if these profiles were related to nocturnal variables and sleepiness.

All participants underwent full overnight PSG in the sleep laboratory. The following measures were included: electroencephalography (EEG), electromyography (EMG) and electro-oculography (EOG), nasal-oral thermistor, abdominal and thoracic respiratory impedance plethysmography, leg electrodes, and finger pulse oximetry. All sleep studies were staged and scored [33] by an experienced sleep scientist unaware of the purpose of the study. The respiratory disturbance index (RDI) was defined using AASM Chicago criteria as the average number of apneas and hypopneas per hour of sleep [27]. A hypopnea was defined as a 50% reduction in either the airflow or abdominal and thoracic respiratory effort signals for greater than

10 seconds in addition to at least 3% arterial oxygen desaturation. An apnea was scored when airflow ceased at the nose and mouth for ≥ 10 seconds [34]. Oxyhaemoglobin saturation (SaO²) during sleep was recorded using pulse oximetry, and the lowest saturation percentage was used for analysis.

Statistical analysis

All data was analysed using Kruskal Wallis Test for non-parametric data to compare demographic, mood scores and polysomnography variables between the three groups, with Mann-Whitney U test for post hoc comparison. Mann-Whitney U test were also used to examine difference in the PLM index between primary snorers and OSA patients. Pearson's correlations were calculated to assess the relationship between nocturnal variables, BMI, mood and sleepiness. Linear regression models were used to assess the relative strengths of any significant associations between depression, nocturnal variables, mood and sleepiness.

Results

Participant Characteristics

Of the 45 patients who were referred to the sleep laboratory, 34 were diagnosed with OSA and eleven were primary snorers (AHI < 5). Subject characteristics and nocturnal respiratory results for OSA patients, primary snorers and healthy controls are displayed in Table 1. There was no significant difference in age between the three groups (P=0.06), however, males were more frequent in the OSA group (χ^2 (2) = 7.07, P<0.05). Body Mass Index (χ^2 (2) = 18.82, P<0.001), RDI (χ^2 (2) = 46.04, P<0.001), and lowest percentage oxygen saturation (χ^2 (2) = 31.49, P<0.001) differed significantly between the three groups. Post-hoc tests revealed that both controls and primary snorers had a lower BMI, lower RDI, and higher nadir oxygen saturation during the night when compared to OSA patients (all P<0.05). There was no significant difference in the PLM index (leg movements per hour) between OSA patients (Mean = 62.2 \pm 52.3) and primary snorers (Mean = 32.2 \pm 29.4) (Wilcoxon = -1.82; P = 0.69). All leg movements were associated with arousals and also

respiratory events, except in two OSA patients and two primary snorers in which leg movements were associated with arousals only.

Table 1 Subject characteristics and nocturnal indices of OSA patients, primary snorers and healthy controls.

	OSA patients	Primary snorers	Controls
	Mean (SEM)	Mean (SEM)	Mean (SEM)
N	34	11	19
Age	51.44 (2.06)	43.73 (3.10)	48.11 (2.14)
Sex (M: F) #	27:7	4:7	12:7
BMI kg/ m² *	32.36 (0.90)	30.09 (1.90)	25.95 (0.79)
RDI*	33.89 (4.62)	3.04 (0.65)	2.54 (0.33)
Arousals/ hour	20.12 (2.65)	11.37 (1.81)	16.54 (1.72)
SaO₂% lowest *	82.79 (1.39)	90.36 (1.02)	92.53 (0.60)

BMI = Body Mass Index (weight (kg)/height (m)²); RDI = respiratory disturbance index; SaO₂% lowest = lowest arterial oxygen saturation percentage. * Primary snorers and controls (p<0.05) were significantly different to OSA patients. # OSA and primary snorers were significantly different to controls.

Mood and sleepiness scores

Depression, mood and sleepiness scores for each group are displayed in Table 2.

There was a significant difference in BDI scores between the groups ($\chi^2 (2) = 9.73$, $P < 0.01$). Post hoc tests indicated that OSA patients and primary snorers reported significantly greater levels of depressive symptoms than controls. On average, OSA patients and primary snorers displayed “minimal” depression levels, based on BDI normative data [29]. However, over 5% of OSA patients reported “severe” depressive symptoms (BDI score > 29), with a further 14.7% indicating “moderate” symptomatology (BDI score 20-28). Twenty percent of the primary snorers compared with 5% of control subjects displayed ‘minimal’ depressive symptoms. Given the gender imbalance between groups, it is important to note that no differences in levels of depression were evident between sexes (Wilcoxon = -0.49; $P = 0.62$).

Significant group differences were found for the POMS dimensions tension ($\chi^2 (2) = 11.50$, $P < 0.005$), depression ($\chi^2 (2) = 14.92$, $P < 0.05$), anger ($\chi^2 (2) = 16.28$, $P < 0.001$) and fatigue ($\chi^2 (2) = 10.73$, $P < 0.01$). Post hoc tests indicated that both primary snorers

and OSA patients reported significantly higher levels of tension, depression, anger and fatigue than control subjects. Group differences were also apparent on the ESS ($\chi^2(2) = 18.67, P < 0.001$). Post hoc tests indicated that both primary snorers and OSA patients reported significantly greater levels of sleepiness when compared to controls. Twenty-one of the 34 (61.8%) OSA patients reported pathological subjective sleepiness (ESS >11; [28]).

Table 2 Differences in mood and sleepiness scores between the OSA patients, primary snorers and healthy controls

Mood Measures	OSA patients	Primary snorers	Controls
	Mean (SD)	Mean (SD)	Mean (SD)
BDI *	10.44 (8.90)	10.64 (6.30)	4.32 (3.37)
POMS tension *	10.03 (5.94)	10.45 (7.10)	4.91 (4.32)
POMS depression *	8.56 (8.82)	10.27 (9.76)	2.42(6.48)
POMS anger *	7.29 (6.36)	9.27 (8.72)	2.49 (5.11)
POMS vigor	13.53 (5.87)	13.36 (4.70)	13.19 (6.16)
POMS fatigue *	13.79 (7.28)	13.45 (9.06)	7.05 (4.63)
POMS confusion	7.85 (4.92)	8.27 (5.83)	6.25 (3.96)
ESS *	11.06 (5.47)	9.36 (5.59)	4.58 (2.32)

BDI = Beck Depression Inventory; POMS = Profile of Mood States, ESS = Epworth Sleepiness Scale
 * OSA patients and primary snorers were significantly different compared to controls ($p < 0.05$).

Correlation and regression analyses

Correlational analyses were performed to identify if any significant relationships existed between mood scores, nocturnal variables and subjective sleepiness ratings (ESS). Sleepiness ratings were significantly associated with the POMS subscales tension, depression, anger, fatigue and confusion (Table 3). Similarly, BDI scores were significantly correlated with all the POMS sub-scales. Further to this, BDI scores were significantly associated with ratings of sleepiness on the ESS. Nocturnal variables were not significantly associated with any mood or sleepiness ratings, however there was a significant positive association between BMI and depression scores (Table 4).

Given the identified significant overlap between the measure of depression, sleepiness, and mood and the lack of association with the nocturnal variables, the sleepiness and mood variables (apart from the depression sub-scale of the POMS due to the conceptual overlap) were entered into a hierarchical linear regression analysis to ascertain which of these measures best predicted levels of depression. With depression scores as the dependant variable and the sleepiness and POMS scores as the independent variables, a stepwise regression analysis was conducted. The first significant model to emerge from the stepwise regression analysis comprised of the fatigue sub-scale of the POMS, which explained 43% of the variance in BDI scores ($F(1, 63) = 46.83, P < 0.001$) and the addition of the confusion sub-scale of the POMS explained a further 5.5% of the variance ($F(2, 63) = 28.73, P < 0.001$).

Table 3 Correlations between Depression, Mood and Sleepiness

	BDI
POMS – Tension	0.62*
POMS – Depression	0.65*
POMS – Anxiety	0.44*
POMS – Vigor	-0.43*
POMS – Fatigue	0.66*
POMS – Confusion	0.63*
Epworth Sleepiness Scale	0.38*

BDI = Beck Depression Inventory; POMS = Profile of Mood States; * = $p < 0.01$

Table 4 Correlations between BMI and Nocturnal variables and Subjective Ratings of Mood and Sleepiness

	BMI	RDI	SaO₂%	AI
BDI – Total Score	0.26 [#]	0.13	-0.17	0.13
POMS – Tension	0.24	0.12	-0.24	-0.01
POMS – Depression	0.21	0.11	-0.21	-0.13
POMS – Anxiety	0.18	0.09	-0.13	-0.07
POMS – Vigor	0.08	0.03	-0.18	-0.14
POMS – Fatigue	0.21	0.12	-0.22	-0.04
POMS – Confusion	0.07	-0.03	-0.08	-0.10
Epworth Sleepiness Scale	0.34*	0.50*	-0.48*	0.07

BDI = Beck Depression Inventory; POMS = Profile of Mood States, BMI = Body Mass Index; RDI = respiratory disturbance index; SaO₂% = lowest arterial oxygen saturation percentage; AI = arousal index. N = 63; # = $p < 0.05$; * = $p < 0.01$

Discussion

This study prospectively investigated the incidence of depression in a group of OSA patients, primary snorers and controls, and examined the possible factors which contribute to this depressive symptomatology. The two major findings of this study were firstly that all patients attending the sleep laboratory, regardless of their OSA diagnosis, reported significantly higher fatigue, daytime sleepiness and depressive symptomatology when compared to a healthy control group. Secondly, the level of fatigue reported by these patients was the primary contributor to their depressive symptoms.

Of the OSA patients, over 20% reported moderate to severe depression, which is consistent with other reports of between 7% and 58% of OSA patients with significant depressive ratings [6, 13, 35]. Interestingly, a proportion of the primary snorers in the current study also reported moderate to severe depressive symptomatology, whilst no control subjects reported these levels of depression. This indicates that depression may be present in people attending the sleep laboratory, regardless of the degree of OSA severity.

Findings from the correlational analyses failed to show any significant association between nocturnal OSA variables (RDI, arousal index, lowest SaO₂%) and depressive symptomatology, consistent with previous studies [13, 15, 17, 25]. However, BMI was significantly associated with depression scores, in line with previous reports. Regression analysis revealed that the degree of depressive symptoms was predicted by levels of fatigue and confusion. This study was the first to assess nocturnal variables, subjective sleepiness ratings, mood and depression scores in OSA patients and primary snorers, compare these scores to a control group, and determine that fatigue was the strongest predictor of depression.

The separate impact of sleepiness and fatigue on depressive symptoms in OSA has been examined previously [13, 25]. The current study included both a measure of fatigue and sleepiness into the regression model to determine which factor predicted the most variance in depressive scores. The fatigue symptoms reported by patients

largely accounted for the depressive symptoms, regardless of disease severity, explaining nearly half the variance in depression scores. Similarly, Bardwell et al. (2003) found that depressive symptoms accounted for approximately 40% of the variance in fatigue reported in OSA patients after apnoea severity was taken into account [25]. In addition to these findings, levels of both depressive symptoms and fatigue have been found to be attenuated by CPAP treatment [36-37], further supporting the existence of an interaction between these symptoms within sleep disturbed populations.

OSA patients and primary snorers did not differ significantly in daytime somnolence and mood, despite differences in nocturnal indices. This raises the possibility that there may be some other underlying cause for the hypersomnolence experienced by primary snorers presenting for clinical assessment. The PLM index was not significantly different between the patient groups, although there was a trend to a higher PLM index in the OSA group. The PLM index is similar to that reported in other OSA populations [38]. In most cases, these leg movements were associated with arousals and respiratory events, thus we do not believe that these patients had a diagnosis of PLM disorder. Two of the OSA patients and two primary snorers had PLMs associated with arousals only that may have contributed to daytime somnolence. Patients with a high arousal index and low RDI in the presence of significant snoring have previously been described as having Upper Airway Resistance Syndrome [39], which could contribute to sleepiness.

Limitations

There are a number of limitations of the current study which should be addressed. The findings of the current study are limited by the severity of OSA patients used. Patients with a greater severity of OSA may have greater functional impairment and report higher daytime sleepiness than the patients used in the current study. Significant differences between primary snorers and control subjects on depression and mood scores were observed, but given the small group sizes, and the inherent referral bias of recruiting at sleep clinics [5], this finding should be interpreted with caution.

It has been noted previously that women tend to be under diagnosed for OSA, due to atypical symptoms [40]. Further, there is a greater incidence of depression amongst

females in the general population [41]. Although no differences were observed in levels of depression between males and females in the current study, these findings should be interpreted with caution due to the greater number of females in the primary snorers group.

Another possible confounder affecting the relationship between OSA and depression, which may also interact with gender, is obesity [3, 5]. Indeed a significant association between BMI and depression scores emerged in the current study, however this did not influence the relationship between fatigue and depression in a separate analysis. Future studies should attempt to control for the possible confound of obesity when examining the relationship between OSA, depression and fatigue.

Conclusion

Taken together, the findings that primary snorers and mild OSA patients have similar levels of depressive symptoms, which are primarily driven by reported levels of fatigue rather than nocturnal factors, have important clinical implications. Utilisation of clinical scales of fatigue and depression, in addition to excessive daytime sleepiness, should be included in the clinical interview for patients presenting to sleep physicians. Depressive symptoms may also impact upon compliance of treatment for OSA, such as CPAP or weight loss. In situations where a patient does report high levels of depression and or fatigue, it would be important to closely monitor the effectiveness of treatment in reversing not only the physiological signs of sleep apnea, but also the daytime sequelae. These findings also have important clinical implications for physicians reviewing patients with depression who may have a concomitant sleep disorder. Difficulties with sleep could exacerbate depressive symptoms, and potentially affect the efficacy of pharmaceutical treatment.

Although the underlying mechanisms of these mood changes in individuals attending the sleep laboratory is still unknown, we have shown for the first time that fatigue is a significant contributor to the depressive symptoms reported by primary snorers and OSA patients alike. Whether fatigue is a causal factor leading to greater depression in these patients is yet to be determined. Future studies need to include a broader range of measures designed to assess daytime functioning of patients attending sleep laboratories, and examine the attenuation of depression and mood disturbances with

treatment. This would be an interesting and useful area of research which would aid understanding of the nature of the psychological changes associated with sleep disturbance, and would assist practitioners in diagnosis and treatment across different severities of OSA.

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