



CLINICAL REVIEW

Obstructive sleep apnea and depression

Melanie Harris^{a,*}, Nick Glozier^{b,e}, Rajeev Ratnavadivel^{c,f}, Ronald R. Grunstein^{d,g}^a Australasian Sleep Trials Network (funded by the National Health and Medical Research Council), c/o Adelaide Institute for Sleep Health, Flinders University, Adelaide, Australia^b The George Institute for International Health, Sydney University, Sydney, Australia^c Adelaide Institute for Sleep Health, Flinders University, Adelaide, Australia^d Woolcock Institute of Medical Research and National Health and Medical Research Council Centre for Respiratory and Sleep Medicine, University of Sydney, Australia

S U M M A R Y

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There are high rates of depression in people with obstructive sleep apnea (OSA) in both community and clinical populations. A large community study reported a rate of 17% and reports for sleep clinic samples range between 21% and 41%. A large cohort study found OSA to be a risk factor for depression, but we are unaware of any longitudinal study of the reverse association. However correlations have not generally been found in smaller studies. Well-designed longitudinal studies are needed to examine temporal relationships between the two conditions and further research is needed to establish the role of confounders, and effect modifiers such as gender, in any apparent relationship. Symptoms common to OSA and depression, such as sleepiness and fatigue, are obstacles to determining the presence and severity of one condition in the presence of the other, in research and clinically. Sleep clinicians are advised to consider depression as a likely cause of sleepiness and fatigue. Several possible causal mechanisms linking OSA and depression have been proposed but not established. Patients who have depression as well as OSA appear worse off than those with OSA only, and depressive symptoms persist in at least some patients in short term studies of treatment for OSA. Direct treatment of depression in OSA might improve acceptance of therapy, reduce sleepiness and fatigue and improve quality of life, but intervention trials are required to answer this question.

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Introduction

Obstructive sleep apnea (OSA) is a common disease, characterised by repetitive upper airway obstruction during sleep and associated with increased morbidity and mortality and diminished quality of life. Depression, a major cause of disease burden and a cardiovascular risk factor, appears to be prevalent in OSA and it has been proposed that depression may be caused by OSA pathology or its symptoms. Existing literature on the prevalence, cause and treatment of depression in OSA is copious but fragmented, making it difficult to assess research to date on the underlying relationship between the two conditions and the impact of treatments in patients with both conditions. This paper therefore reviews the prevalence of depression in OSA, evidence for causal links, possible causal mechanisms, and the impact of OSA

and depression therapies. It then highlights practice points and research needed, shown by the review.

Methodological issues

Several methodological issues need to be taken into account in reviewing this field. These include definitions of depression in the OSA-depression literature, how depression is measured, possible confounders to be considered when assessing prevalence and correlational studies, and referral and reporting biases.

Definition and measurement issues

Multiple measurement instruments

The use of different techniques to identify both depressive symptoms or disorder and sleep breathing disorders are one source of possibly misleading variation between studies. For example, in prevalence studies depression has been identified using the Sleep-EVAL expert system, a self-completed measurement scale Beck Depression Inventory (BDI), self-report of suffering from depression and clinician diagnosis of depression, the last of these generally indicating lower prevalence in other settings. More consistency

* Corresponding author. Tel.: +61 8 8404 2323; fax: +61 8 8404 2101.

E-mail addresses: melanie.harris@flinders.edu.au (M. Harris), nglozier@george.org.au (N. Glozier), rajeev.ratnavadivel@health.sa.gov.au (R. Ratnavadivel), rrg@med.usyd.edu.au (R.R. Grunstein).^e Tel.: +61 2 9993 4575; fax: +61 2 9657 0301.^f Tel.: +61 8 8276 9666; fax: +61 8 8277 6890.^g Tel.: +61 2 9515 8630; fax: +61 2 9515 7070.

Nomenclature

AHI	Apnea Hypopnea Index
BDI	Beck Depression Inventory
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression Scale
CPAP	Continuous positive airway pressure
EDS	Excessive daytime sleepiness
HAD	Hospital Anxiety and Depression scale
HAD-D	Hospital Anxiety and Depression - depression scale
OA	Oral appliance
OSA	Obstructive sleep apnea
PSG	Polysomnography
RDI	Respiratory Disturbance Index
REM	Rapid eye movement
SCL-90	Symptom Checklist - 90
SIGH-SAD-SR	Hamilton Depression Rating Scale – Seasonal Affective Disorders Self-Rating Scale

in choice of measures would allow for more reliable comparisons and syntheses.

Diagnosis vs. symptom counts

Stringent identification of depression relies on structured medical interviews using Diagnostic and Statistical Manual of Mental Disorders, DSM-IV classification rules e.g., the Schedules for Clinical Assessment in Neuropsychiatry or Composite International Diagnostic Interview. The DSM-IV appears to be relatively unaffected by the presence of some comorbid chronic illnesses,¹ and in using DSM-IV interviewers are instructed to disregard symptoms directly attributable to the comorbid illness. However, diagnosis, especially in the primary care setting is often less formalised.² Specialist resources required for firm diagnosis of both OSA and depressive illness are also not feasible for large-scale prevalence studies therefore rating scales of symptoms measures must be used and these give higher rates.

Symptom specificity

Common symptoms in OSA and depression are obstacles for determining the presence and severity of one condition in the presence of the other, both in research studies and clinically. Overlapping complaints include fatigue, loss of interest, decreased libido and poor concentration.³ By including complaints like these, several frequently used scales of depressive symptoms may not be valid for use in some physical disorders^{4,5} including OSA.^{6–8} Attempts to overcome the difficulty of measuring depressive symptoms where OSA is likely to produce similar symptoms range from study-specific modifications to existing scales⁹ to suggestions that only cognitive features of depression, such as feelings of guilt or worthlessness, self-blame ruminative thoughts and crying, should be used in OSA.¹⁰ While commonly used depression scales have been validated for various patient groups, specifically the Hamilton Hospital Anxiety and Depression Scale-depression scale (HAD-D)¹¹ there do not appear to be validation studies in OSA despite the frequent assessment of mood in OSA research. It appears that studies are needed to evaluate the validity of various depression scales, and variants, in OSA. Overlapping symptoms can also add confusion to clinical diagnosis of both depression and OSA.

How cardinal are “cardinal” symptoms?

Though excessive daytime sleepiness (EDS) and fatigue are regarded as signs of OSA, empirical evidence does not support a strong association^{12,13} and sleep physicians also need to be alert to

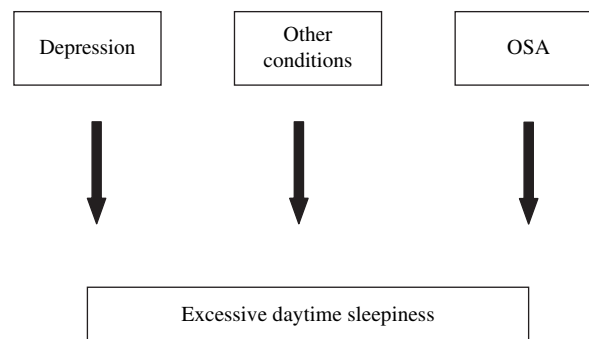


Fig. 1. Causes of excessive daytime sleepiness.

other causes of these symptoms. Fatigue in particular is amongst the most common of complaints in primary care, and associated with an increased likelihood of psychiatric disorders.¹⁴ Bixler and colleagues¹⁵ in a USA cohort found depression and then body mass index (BMI), age, sleep duration, diabetes, and smoking to be the most significant risk factors for EDS, as measured by two study-specific questions about daytime sleepiness. Presence of OSA (defined as Obstructive apnea or hypopnea index ≥ 15) did not make a significant contribution to the regression model. Sleepiness was also related to depression but not AHI and less strongly to oxygen saturation in a Swiss study of snorers, OSA patients and controls.³ Similarly, in two studies of untreated OSA patients in the USA, depressive symptoms were stronger predictors of fatigue than OSA severity and, individually, neither RDI (respiratory disturbance index) nor oxygen saturation were significantly predicted by fatigue.¹⁶ On the other hand, a study of 230 Japanese male patients showed AHI and personality characteristics, but not depression scores, as related to daytime sleepiness.¹⁷

Relationships suggested by these studies are represented in Fig. 1.

Sleep clinicians are advised to consider mood factors (such as depression) and metabolic factors (such as obesity and diabetes) as perhaps more likely causes of sleepiness and fatigue than OSA and to be liberal in making referrals for assessments of these factors.^{15,18,19}

Possible confounders and effect modifiers affecting prevalence and correlational studies

Any relationship between OSA and depressive symptoms found in prevalence studies and correlation studies might be at least partially due to uncontrolled confounding factors. Obesity is the most commonly suggested confounder but depression and obesity do not have a straightforward or consistent association,²⁰ as has also been found in some OSA populations.¹⁰

Any confounding by BMI may operate differently for men and women. Aloia and colleagues⁷ measured sleep variables, BMI and depressive symptoms in a group of men and women with moderate to severe OSA (clinician-diagnosed) and without major psychiatric disorder. For the 61 men in their sample RDI was independently related to the BDI somatic dimension. For the 32 women, however, there was an independent relationship between the cognitive dimension of the BDI and BMI.

While obesity is one possible confounder there may also be relationships between depression and medical co-morbidities of OSA. Bardwell and colleagues²¹ studied 72 male and female subjects with sleep apnea. They found that associations between mood variables and sleep variables disappeared after controlling for age, BMI, and hypertension. These authors pointed out that hypertension is rarely included in correlation studies and confounding by this variable may explain disparities in other studies.

An alternative view is that as OSA has been shown to contribute to hypertension²² no adjustment should be made. Ohayon's²³ large European cross-sectional study found that the association between sleep breathing disorder and major depression persisted even when obesity and hypertension were taken into account. Other factors associated with depression, such as age, gender, marital status, education, and income²⁴ and other chronic medical illnesses²⁵ could be included as possible confounders in observational studies of depression in OSA.

Alcohol consumption is associated with depression and warrants consideration as a possible confounder or effect modifier in studies of relationships between depression and OSA. Though acute administration of alcohol to subjects with at least mild OSA has increased apneas and hypopneas in some experiments,^{22,26} epidemiological studies are inconsistent in finding associations between self-reported alcohol use and OSA.^{22,27} A recent Swedish study showed blood alcohol levels in OSA patients consistent with usual population rates of alcohol abuse, supporting earlier findings in the UK and Hawaii.²⁸ Overall, therefore, the case is not strong for a direct relationship between alcohol use and development of OSA, though for people who have the condition, alcohol may worsen OSA symptoms.

Physical exercise is a further candidate confounding variable. Exercise is associated with both reduced depressive symptoms and reduced prevalence of OSA, at least in observational studies.^{29,30}

Different gender compositions in study samples may introduce further variation by effect modification. Studies in OSA which have reported findings by gender show higher rates of depression in women than in men.^{31–33} This reflects a more general finding for prevalence of depression,³⁴ and studies in OSA should now report by gender.

It is evident that possible confounding and effect modification should be taken into account in assessing observational studies. It is also evident that further research is needed to establish the role of confounders in the relationship between OSA and depression, and that studies should include sufficient numbers of both women and men and report results separately for both. An important issue is that analyses rarely test for effect modification, assuming simple linear associations and confounding. As shown above interactions with gender at least should be considered.

Referral and reporting biases

A further methodological issue to be noted in studies of clinical populations is referral bias. For patients who have both OSA and depression, referral bias might operate to increase detection of the other condition, if frequent consultations prompt further referrals, or to reduce detection of the other condition, if primary care physicians attribute symptoms to the first condition only. Clinical OSA populations are also more likely to be impaired which would raise the likelihood of a depression. This bias would explain a differential association of OSA and depression from correlational studies based in clinical populations.

Another possible bias is symptom over-reporting in people with depression. For instance those with depression have a greater tendency to rate sleep more poorly compared to PSG measures than people without depression.³⁵ Studies relying on self-reported measures of sleep, therefore, may provide biased data on relationships between objective sleep measures and depression.

The prevalence of depression in OSA

Population and community prevalence

There are few reports of purpose-designed studies to determine the prevalence of depression comorbid with OSA in general

or primary care populations. A population survey sampling 18,980 adults from 5 European countries used the "Sleep-EVAL" expert system in telephone interviews to identify sleep and depressive disorders.²³ This system has not been extensively validated as a screen for depression but is based on Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, criteria.²³ Among the 857 people identified as having OSA or other type of breathing related sleep disorder, the prevalence of major depressive disorder was 17%, while the prevalence for the whole sample was 4.3%. A prevalence study using diagnoses recorded in a four year period of the healthcare database for USA Veterans Health Administration beneficiaries, found that of 4,060,504 unique cases, 118,105 had clinician-diagnosed OSA and of these, 21.8% also had clinician-diagnosed depressive disorder.³⁶ The prevalence of depression was 9% in non-apneics ($P < 0.0001$). In the Hordaland Health Study of over 7,000 working middle aged Norwegians, the 440 participants with OSA symptoms had significantly greater mean depression rating scores.³⁷ The background prevalence of depression among people without OSA in these large-scale studies is consistent with earlier findings of 3–5% in community settings and 5–10% in primary care³⁸ in the USA, supporting the credibility of reported higher prevalence among people with OSA.

Rates in clinical populations

Other prevalence studies have looked at people entering sleep clinics who were then diagnosed with OSA. These studies have generally shown high rates of depression or depressive symptoms in OSA patients. Vandeputte and deWeerd³⁹ found 41% (95% CI 37–44%) of 167 Dutch sleep clinic referrals diagnosed with OSA according to American Sleep Disorders Association classification had a BDI score of 10 or more, commonly used as indicative of probable depression. Self-reported depression rates among 406 people diagnosed with OSA (Apnea Hypopnea Index (AHI) ≥ 15 or AHI ≥ 5 with other problems) in a USA sleep clinic were 30% overall, 38% for women and 26% for men.³¹ Two further studies also provided data by gender for clinical samples. Of 130 women with "documented breathing disorders" randomly selected from a Canadian OSA clinical database 21% had a self-reported previous diagnosis of depression compared with 7% of 130 matched men from the same database.³³ Of 29 women entering a USA sleep clinic and diagnosed with OSA according to American Academy of Sleep Medicine Task Force 1999 recommendations, 28% were categorised as having moderate to severe depression (BDI > 19) compared with 6% of 92 men given the same diagnosis.³² Variation in rates would be expected with differently composed clinical populations from different communities, and further variability is added with the use of different measures for depression or different cut off points. However, these studies report high rates of depression or depressive symptoms in people with OSA and point to higher rates among women in clinical samples.

Rates of depression have also been extracted from 24 reports of studies in OSA to give a range of 7–63%.⁴⁰ However, most of the original studies were designed as experimental or correlation studies rather than prevalence studies. This range therefore reflects rates in small clinical samples after the application of differing sets of inclusion/exclusion criteria and not the prevalence of depression in people with OSA in populations or usual rates of depression in clinical OSA populations.

In summary, prevalence studies have shown high rates of depression among people with OSA in both community and clinical populations. There is variation in reported rates, some of which will reflect underlying differences between populations and some of which may be attributable to the confounders, effect modifiers, biases and measurement issues discussed above.

Correlational studies

While depression or depressive symptoms are prevalent in OSA populations, they may stem from factors other than OSA. A direct link between OSA and depression would be further supported by evidence of dose–response and temporal relationships, with possible confounding factors investigated.

Relationships in severity of disease – cross-sectional studies

A relationship between severity of OSA and severity of depressive symptoms would be expected if the two conditions were directly linked. In a USA sample of 190 women and 165 men there was no relationship between depression, measured by the Center for Epidemiologic Studies Depression Scale (CES-D) or by atypical depression items from the Hamilton Depression Rating Scale–Seasonal Affective Disorders Self-Rating (SIGH-SAD-SR) scale, and OSA severity, measured by desaturations.⁴¹ Similarly, Pillar and Lavie's⁴² large study of 2271 clinic referrals (RDI range <10 to >33) in Israel found no association for males between RDI and depressive symptoms scores using the Symptom Checklist-90 (SCL-90). While in women depression scores were higher in those with severe sleep apnea, there was no simple severity relationship across categories of sleep breathing disorder. Simple snorers, for example, reported more depressive symptoms than those with mild apnea. Smaller studies have also found little or no correlation between the severity of mood symptoms and the severity of apnea, potentially as a consequence of being underpowered. One study looked at a group of 98 USA male veterans with OSA diagnosed by International Classification of Sleep Disorders criteria. Although 37.5% had BDI scores in the “clinically significant range” of 15 or more, there was no difference between this group and those with lower BDI scores for either AHI or SaO₂ nadir, and no non-significant trends.¹⁰ A Polish study ($n = 63$) also found no significant differences between men with and without OSA for BDI or CES-D (with mean BDI scores highest in the control group).⁴³ Another study of HAD-D scores in 44 Swiss OSA patients and 16 snorers found no significant correlation with AHI (and a trend, $p = 0.06$, towards a negative relationship) but did find a significant positive correlation between mean low oxygen saturation and HAD-D score.³ In a USA clinical sample of 61 men and 32 women, with major psychiatric conditions screened out, there was a significant relationship of RDI with BDI total score and with BDI somatic but not cognitive dimension, a surprising finding given the limited variability of the BDI score in this highly selected group. Analysis by gender, however, showed an independent relationship only for men between RDI and the somatic, but not the cognitive, dimension of the BDI. For women, BMI but not RDI was related to only the cognitive dimension of the BDI.⁷ Overall, however, studies have generally failed to find a symptom correlation. It should be noted that lack of demonstrated correlation does not necessarily mean there is no link between the two conditions. For example, severity of depression is not necessarily related to number of symptoms as measured in depression scales or the two conditions could be a result of the same underlying phenomenon, and a further possibility is a relationship in some but not all individuals due to genomic variation.⁴⁴

A study of an older community sample showed different results for men and women. The Cardiovascular Health Study cohort, comprising 5201 USA residents aged 65 and older, measured self-reported partner-observed apneas and assessed depressive symptoms using the CES-D. Results of this study were reported by gender and an association between depression and observed apneas was found in women but not in men.⁴⁵ A weakness of this study is reliance on witnessed apneas, a weak predictor of OSA.⁴⁵

Relationships in disease onset

Stronger evidence of a causal link is obtained from prospective longitudinal studies. One large-scale cohort study has shown an increased risk of developing depression as OSA develops or worsens, and a dose–response relationship between severity of OSA and, importantly, odds of developing depression.⁹ Polysomnography (PSG) and a modified Zung Depression Scale were administered to 1408 community subjects at multiple 4-year intervals. Depression was defined as Zung score of at least 50 or antidepressant use. Moving from one OSA severity level to a higher one during a 4-year period was associated with a 1.8 odds ratio of developing depression during the same period. There was also a consistent severity relationship. In models controlled for age, BMI, alcohol consumption and history of cardiovascular disease, people within each OSA severity category were at greater risk of having developed depression than those in less severe categories. While purely cross-sectional studies have not shown clear severity relationships, 4-year interval data in this large adult population sample did show an association between OSA severity and risk of developing depression, as well as development of depression alongside worsening of OSA.

Retrospective studies have also shown that patients diagnosed with OSA are at increased risk of having had a diagnosis of depression.^{46,47} These studies do not show the order of onset of actual disease however, and diagnoses of depression may have been given incorrectly on the basis of symptoms that are common to both conditions.

Longitudinal studies are still needed to determine whether one condition follows the other in different contexts.

As noted earlier, possible explanations for differing findings among observational studies include hidden confounders or effect modifiers in some study samples.

Correlational studies are summarised in Table 1.

Impact of therapies

Impact of OSA therapies on depression

If there is a direct causative link between OSA and the onset of depression, then depression would be expected to improve with successful treatment of OSA. While improvements in depression scores have been reported in some^{6,48–50} but not all⁵¹ studies without placebo arms, the weakness of such uncontrolled designs has been highlighted by reports of a large placebo effect for depression scores both generally⁵² and in OSA.^{53,54} A recent Cochrane meta-analysis covered randomised controlled trials published before mid 2005.⁵⁵ This meta-analysis confirmed that continuous positive airway pressure (CPAP) therapy was effective in reducing sleepiness and improving quality of life measures in OSA. Results for the Hospital Anxiety and Depression Scale were also extracted from five clinical trials comparing CPAP with placebo and while pooled fixed effects significantly favoured CPAP, there was no significant effect of CPAP treatment after the application of random effects modelling. In addition to these trials employing HAD-D, a further study⁵⁶ included in the Cochrane review employed the Geriatric Depression Scale. No significant difference was found between control and intervention arms for change in this scale. Two new randomised controlled trials^{54,57} published since the Cochrane review found no mood improvement associated with CPAP. However, both studies measured outcomes after only 2 weeks of CPAP treatment, and intervention studies in depression typically take 4–6 weeks to show any significant difference between treatment and control arms, primarily due to a large early placebo effect operating in both arms. Additionally, one study⁵⁴ employed the Profile of Mood States scale rather than a specific

Table 1
Summary of correlational studies.

First author/date	Study population	Depression measure/s	OSA measure/s	Study conclusions
<i>Cross-sectional studies</i>				
Enright/1996 ⁴⁵	5201 community sample 65 years and older (2239 men)	CES-D.	Self-reported partner-observed apneas	Association between depression and observed apneas found in women but not in men.
Kripke/1997 ⁴¹	Community sample of 355 (165 men)	CES-D or items from SIGH-SAD-SR	Desaturations	No relationship
Pillar/1998 ⁴²	2271 referrals (1977 men) to sleep clinic	SCL-90 (HAD-D)	RDI	No consistent relationship
Sforza/2002 ³	44 OSA patients and 16 snorers, genders not given		AHI, mean low oxygen saturation	No correlation between AHI and HAD-D score. Positive correlation between mean low oxygen saturation and HAD-D score
Smith/2002 ⁴⁶	Records of 773 patients with OSA (599 men) and matched controls from the general population	Physician diagnosis	Physician diagnosis	OSA patients had odds ratio 1.4 (95% CI, 1.0 to 1.9) of past depression
Aloia/2005 ⁷	Sleep clinic sample 93 (61 men)	BDI	RDI	Relationship of RDI with BDI total score and with BDI somatic dimension. By gender, independent relationship between RDI and somatic dimension only for men.
Farney/2004 ⁴⁷	Records of 212,972 patients (102,614 men)	Prescription for antidepressant medications	Physician diagnosis	Likelihood of having OSA increased in depression.
<i>Cohort study</i>				
Peppard/2006 ⁹	1408 community subjects (788 men)	Modified Zung Depression Scale or antidepressant use	PSG	1.8 odds ratio of developing depression within a 4-year interval as OSA develops or worsens. Dose-response relationship between severity of OSA and odds of developing depression

AHI = Apnea Hypopnea Index; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; HAD-D = Hospital Anxiety and Depression - depression scale; OSA = Obstructive sleep apnea; PSG = Polysomnography; RDI = Respiratory Disturbance Index; SCL-90 = Symptom Checklist - 90; SIGH-SAD-SR = Hamilton Depression Rating Scale - Seasonal Affective Disorders Self-Rating Scale

depression instrument and the other,⁵⁷ using Brief Symptom Inventory depression subscale, may have been underpowered. Of interest is a comparison in one of these studies⁵⁷ between CPAP and oxygen therapy. While the sham CPAP group showed no improvement in depression scores, and the therapeutic CPAP group showed a non-significant trend to improvement, the oxygen therapy group showed significant improvement. Investigators suggest that for patients unable to adhere to CPAP, nocturnal oxygen supplementation may improve psychological functioning.

An ongoing large-scale trial ($n = 1100$) in moderate to severe OSA, the Apnea Positive Pressure Long-term Efficacy Study or APPELES, currently being conducted in the USA, may provide more information. A secondary aim of APPELES is to show whether CPAP improves depression scores in moderate to severe OSA. APPELES enrolment includes patients with clinical depression therefore may show whether or not CPAP therapy is effective against depression that is comorbid with OSA. If CPAP is ineffective in treating clinical depression in OSA, large-scale trials will be needed to test other interventions.

Oral appliance (OA) therapy is an alternative to CPAP which improves subjective sleepiness and sleep disordered breathing.⁵⁸ Unfortunately, few trials of OA therapy have included depression measures. One trial⁵⁹ showed similar BDI improvement for OA, CPAP and placebo from a baseline mean of 9.2. Another⁶⁰ showed significant improvement in the somatic but not cognitive component or total score of the BDI with OA, with baseline mean only 5.8.

Overall, evidence to date suggests that depressive symptoms may persist in at least some patients receiving CPAP or other treatment for OSA.

Varied results in controlled trials on the effectiveness of CPAP and OA treatment in reducing depressive symptoms may be due to differences between study designs, such as duration of intervention and choice of control condition, to differences between study populations in gender mix and initial severity of OSA and depression, or to measurement problems. Research could be conducted to isolate any variables which are associated with reduction of depressive symptoms when OSA is treated. As

clinical trials to date have included patients with depression scores mainly in the non-clinical range where there may be floor effects of any intervention, trials are needed to assess the effectiveness of CPAP in alleviating clinically relevant levels of depression. On the other hand, a reduction in “depressive” symptoms across the severity range may imply that the CPAP is having an effect upon epiphenomena such as tiredness and motivation rather than depression *per se*.

Therapies for depression

Higher rates of depressive disorder and depressive symptoms are a common finding in virtually every chronic medical illnesses, particularly those associated with pain and disability with causation now being proposed in both directions and somatic symptoms strongly associated with depressive symptoms.^{25,61,62} Active monitoring, and treatment of depressive illness which results in undue distress or greater impairment, is proposed both for chronic illnesses generally^{25,61,62} and in sleep medicine where comorbid depression might reduce patient adherence to CPAP as well as contribute to disease burden.^{18,19,63} Trials are now being conducted to assess the effect of enhanced depression care on symptom burden, self-care and costs in chronic medical illnesses. Some^{64,65} though not all¹ trials completed in other conditions have shown benefits. Such trials could be considered in OSA, especially as CPAP alone does not appear to reliably treat co-morbid depression. In addition, the possibility of worse chronic illness outcomes for patients who do not respond to treatment for comorbid depression⁶⁶ has not been examined in OSA.

Altered sleep architecture, including increased rapid eye movement sleep (REM) is seen in depression⁶⁷ and further sleep changes may be caused by some antidepressive medications. Reduced REM sleep percentage, found in many studies of normal and depressed subjects who have been given common classes of antidepressants,⁶⁸ is also found in OSA subjects, though without an apparent effect on apnea frequency.⁶⁹ Both tricyclic and selective serotonin reuptake inhibitor antidepressants may also lower sleep efficiency in patients with OSA.⁶⁹ Data on differential effects of

antidepressant drugs is available, at least for non-OSA subjects, to assist with choice of depression therapy in OSA.⁶⁸

The impact of depression on OSA

Comorbid depression has been found to impact adversely on self-management, treatment adherence and functioning and to increase symptom perception and health care cost in other chronic medical illnesses.^{38,62} Though there has been little research on the impact of depression in OSA, patients who have depression as well as OSA also appear worse off than their counterparts with OSA only. OSA patients with high levels of depression are those with most daytime sleepiness,¹⁸ fatigue,¹⁶ and lowest quality of life scores.⁷⁰ Reports are inconsistent on CPAP compliance. In a pre-post study of 54 new OSA patients, neither pre-CPAP depression scores nor post-CPAP improvement in these scores were related to use of CPAP.⁷¹ However, in a questionnaire study of 178 patients who had earlier been given CPAP, depression was associated with low compliance.¹⁸ Treatment of depression might improve acceptance of CPAP, reduce sleepiness and fatigue and improve quality of life, but this remains to be tested.

Possible basic mechanisms

If the observation from one longitudinal study is repeated, showing OSA to be a risk factor for the onset of depression, basic mechanisms will be of interest. Existing data suggests some potential pathophysiological links.

Effects of sleep fragmentation and hypoxia on mood

Noting that early studies showing links between depressive symptoms and sleep fragmentation or hypoxia in OSA had small numbers of patients and did not control for likely confounders, Bardwell²¹ with $n = 72$ showed no relationship between depression and either sleep fragmentation or hypoxia when BMI and hypertension were controlled. Bardwell and colleagues⁵⁷ later compared the effects of CPAP and oxygen therapy on depressive symptoms in a controlled randomised trial in 38 people with OSA. While other arms showed no significant effect, the oxygen therapy arm showed significant reduction in psychological symptoms. Authors concluded that in patients with OSA hypoxaemia may play a stronger role than sleep disruption in depression. In contrast, a case-control study⁷² showed psychological symptoms to be correlated with sleep fragmentation but not with oxygen desaturation. However, this conclusion was drawn using the 10 most commonly checked items on the SCL-90 rather than the depression subscale.

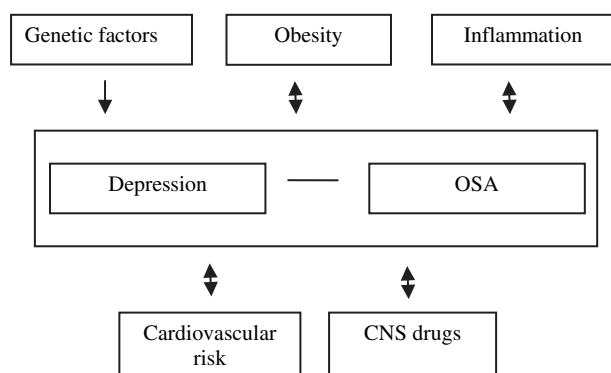


Fig. 2. Possible shared pathways for depression and OSA.

Possible common neurotransmitter disturbances

Obstructive sleep apnea is associated with elevated levels of the cytokines IL 6 and tumour necrosis factor.^{73,74} These cytokines have been proposed as the mediators of daytime sleepiness in this condition. Administration of a tumour necrosis factor antagonist has been shown to dramatically reduce the level of daytime sleepiness in patients with obstructive sleep apnea.⁷⁵ Major depression has also been shown to be associated with an immune response involving proinflammatory cytokines IL 1, IL 6 and interferon.⁷⁶ While these studies involve small numbers of subjects and do not imply causation, they do suggest a possible shared pathway between these conditions. Further, obesity, particularly visceral

Practice points

- Clinicians should be aware of high rates of depression among people with OSA in both community and clinical populations, with rates potentially higher in women than in men.
- Depressive symptoms may better explain EDS and fatigue than measures of OSA severity.
- Depressive symptoms may persist in at least some patients receiving CPAP or other treatment for OSA.

Research agenda

- Greater consistency in techniques to identify depressive disorder and sleep breathing disorders will allow for comparisons between studies and better research syntheses.
- Symptoms common to both depression and OSA mean that commonly used depression scales may not be valid in OSA. Formal assessment of depression scales could identify a scale or variant of acceptable validity.
- With different rates of depression and perhaps different causal mechanisms for men and women, results of observational and experimental studies should be reported by gender.
- Further research is needed to establish the role of a larger range of possible confounders in explaining the prevalence of depression in OSA.
- Short and, if needed, longer-term longitudinal cohort studies are needed to show whether or not OSA increases the risk of later developing depression and vice versa.
- Suitably powered trials are needed to assess the effectiveness of CPAP, and possibly other treatment options, in OSA populations with greater levels of depression than in most trials to date.
- Research is needed to determine whether, and to what extent, comorbidity has a greater impact on individuals, family, adherence and mortality.
- Pathophysiological studies should clarify whether the high rates of comorbidity reflect causation or two conditions which are manifestations of common underlying alterations.
- Studies are needed to support decisions on how we should treat depression in OSA for example with antidepressants vs. cognitive behavioural therapy (and the effect of such treatment on a range of outcomes including fatigue, sleepiness, and compliance).
- The sequelae of being a nonresponder to treatment for depression should be followed.

obesity is also associated with an elevation in these cytokines and thus might be a confounder.⁷³

Abnormalities in central and peripheral neurotransmission of serotonin have been implicated as a potential cause of major depression.⁷⁷ Serotonin is also thought to be involved in the sleep dependant reduction in output to the upper airway dilator muscles, particularly the hypoglossal nucleus, although this pathway is extremely complex, with multiple receptor subtypes.⁷⁸ The exact role of serotonin in the hypoglossal nucleus has also not been characterised. Again this may suggest a shared pathway.

A further possibility is an as yet uncharacterised underlying causal mechanism for both OSA and depression.

Overall, similar factors may be causative for both OSA and depression, with links between the two still uncertain (Fig. 2)

Chronic illness burden

In addition to specific pathophysiological effects of OSA on the brain, another possibility is that depression in OSA is secondary to the development of a chronic medical illness and its complications and symptoms.³⁸ High prevalence of depressive disorder and depressive symptoms is a consistent finding in chronic medical illnesses,^{25,61} and untreated OSA has been found to reduce quality of life on a par with other chronic diseases of moderate severity.^{22,79}

Discussion

Despite a plethora of studies we still have no clear view of the role of OSA in the causation of depression. Neither do we know whether successful treatment of OSA also improves depressive illness. Depression has not been a primary outcome in trials to date but these trials are now needed, and would focus on subjects with clinical levels of depression with outcomes including validated measures of depression and measures of excessive daytime sleepiness. Markers of individual differences likely to influence responsiveness to depression treatments could also be considered in the design of new studies.^{44,80}

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References

- Lin EHB, Katon W, Rutter C, Simon GE, Ludman JE, Von Korff M, et al. Effects of enhanced depression treatment on diabetes self-care. *Ann Fam Med* 2006;**4**:46–53.
- Coyne JC, Thompson R, Klinkman MS, Nease Jr DE. Emotional disorders in primary care. *J Consult Clin Psychol* 2002;**70**:798–809.
- Sforza E, de Saint Hilaire Z, Pelissolo A, Rochat T, Ibanez V. Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. *Sleep Med* 2002;**3**:139–45.
- Grayson DA, Mackinnon A, Jorm AF, Creasey H, Broe GA. Item bias in the center for epidemiologic studies depression scale: effects of physical disorders and disability in an elderly community sample. *J Gerontol B Psychol Sci Soc Sci* 2000;**55**:P273–82.
- Sodeman E, Lisspers J. Diagnosing depression in patients with physical diseases using the beck depression inventory (BDI). *Cogn Behav Ther* 1997;**26**:102–12.
- Sanchez AI, Buela-Casal G, Bermudez MP, Casas-Maldonado F. The effects of continuous positive air pressure treatment on anxiety and depression levels in apnea patients. *Psychiatry Clin Neurosci* Dec 2001;vol. 55(6):641–6.
- Aloia MS, Arnedt JT, Smith L, Skrekas J, Stanchina M, Millman RP. Examining the construct of depression in obstructive sleep apnea syndrome. *Sleep Med* 2005;**6**:115–21.
- Andrews JG, Oei TPS. The roles of depression and anxiety in the understanding and treatment of obstructive sleep apnea syndrome. *Clin Psychol Rev* 2004;**24**:1031–49.
- Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med* 2006;**166**:1709–15.
- Hashmi AM, Giray N, Hirshkowitz M. Sleep-related breathing disorders and mood disorders. *Sleep Med Clin* 2006;**1**:513–7.
- Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res* 2002;**52**:69–77.
- Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep* 2005;**28**:472–7.
- Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 1999;**159**:502–7.
- Kroenke K, Price RK. Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. *Arch Intern Med* 1993;**153**:2474–80.
- Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab* 2005;**90**:4510–5.
- Bardwell WA, Ancoli-Israel S, Dimsdale JE. Comparison of the effects of depressive symptoms and apnea severity on fatigue in patients with obstructive sleep apnea: a replication study. *J Affect Disord* Jan 2007;vol. 97(1–3):181–6.
- Hayashida K, Inoue Y, Chiba S, Yagi T, Urashima M, Honda Y, et al. Factors influencing subjective sleepiness in patients with obstructive sleep apnea syndrome. *Psychiatry Clin Neurosci* 2007;**61**:558–63.
- Kjelsberg FN, Ruud EA, Stavem K. Predictors of symptoms of anxiety and depression in obstructive sleep apnea. *Sleep Med* 2005;**6**:341–6.
- Santamaria J, Iranzo A, Ma Montserrat J, de Pablo J. Persistent sleepiness in CPAP treated obstructive sleep apnea patients: evaluation and treatment. *Sleep Med Rev* 2007;**11**:195–207.
- Cooke L, Wardle J. Depression and obesity. In: Steptoe A, editor. *Depression and physical illness*. Cambridge: Cambridge University Press; 2006. p. 238–61.
- Bardwell WA, Berry CC, Ancoli-Israel S, Dimsdale JE. Psychological correlates of sleep apnea. *J Psychosom Res* 1999;**47**:583–96.
- Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;**165**:1217–39.
- Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. *J Clin Psychiatry* 2003;**64**:1195–200.
- Akhtar-Danesh N, Landeen J. Relation between depression and sociodemographic factors. *Int J Ment Health Syst*; 2007:1–9.
- Benton T, Staab J, Evans DL. Medical co-morbidity in depressive disorders. *Ann Clin Psychiatry* 2007;**19**:289–303.
- Izumi I, Nasermoaddeli A, Sekine M, Kagamimori S. Effect of moderate alcohol intake on nocturnal sleep respiratory parameters in healthy middle-aged men. *Environ Health Prev Med* 2005;**10**:16–20.
- Moreno CRC, Carvalho FA, Lorenzi C, Matuzaki LS, Prezotti S, Bighetti P, et al. High risk for obstructive sleep apnea in truck drivers estimated by the Berlin questionnaire: prevalence and associated factors. *Chronobiol Int* 2004;**21**:871–9.
- Nerfeldt P, Graf P, Borg S, Friberg D. Prevalence of high alcohol and benzodiazepine consumption in sleep apnea patients studied with blood and urine tests. *Acta Otolaryngol (Stockh)* 2004;**124**:1187–90.
- Daley A. Exercise and depression: a review of reviews. *J Clin Psychol Med Settings* 2008;**15**:140–7.
- Quan SF, O'Connor GT, Quan JS, Redline S, Resnick HE, Shahar E, et al. Association of physical activity with sleep-disordered breathing. *Sleep Breath* 2007;**11**:149–57.
- Wahner-Roedler DL, Olson EJ, Narayanan S, Sood R, Hanson AC, Loehrer LL, et al. Gender-specific differences in a patient population with obstructive sleep apnea-hypopnea syndrome. *Gen Med* 2007;**4**:329–38.
- McCall WV, Harding D, O'Donovan C. Correlates of depressive symptoms in patients with obstructive sleep apnea. *J Clin Sleep Med* 2006;**2**:424–6.
- Sheperdycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep* 2005;**28**:309–14.
- Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. *Br J Psychiatry* 2000;**177**:486–92.
- Rotenberg VS, Indursky P, Kayumov L, Sirota P, Melamed Y. The relationship between subjective sleep estimation and objective sleep variables in depressed patients. *Int J Psychophysiol* 2000;**37**:291–7.
- Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep* 2005;**28**:1405–11.
- Sivertsen B, Overland S, Glozier N, Bjorvatn B, Maeland JG, Mykletun A. The effect of OSAS on sick leave and work disability. *Eur Respir J* 2008;**32**:1497–503.
- Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003;**54**:216–26.
- Vandeputte M, de Weerd A. Sleep disorders and depressive feelings: a global survey with the Beck depression scale. *Sleep Med* 2003;**4**:343–5.
- Saunamaki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. *Acta Neurol Scand* 2007;**116**:277–88.

* The most important references are denoted by an asterisk.

41. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40–64 years: a population-based survey. *Sleep* 1997;**20**:65–76.
- *42. Pillar G, Lavie P. Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbance index. *Chest* 1998;**114**:697–703.
43. Glebocka A, Kossowska A, Bednarek M. Obstructive sleep apnea and the quality of life. *J Physiol Pharmacol* 2006;**57**(Suppl. 4):111–7.
44. Lee C, Morton CC. Structural genomic variation and personalized medicine. *N Engl J Med* 2008;**358**:740–1.
45. Enright PL, Newman AB, Wahl PW, Manolio TA, Haponik EF, Boyle PJ. Prevalence and correlates of snoring and observed apneas in 5201 older adults. *Sleep* 1996;**19**:531–8.
46. Smith R, Ronald J, Delaive K, Walld R, Manfreda J, Kryger MH. What are obstructive sleep apnea patients being treated for prior to this diagnosis? *Chest* 2002;**121**:164–72.
47. Farney RJ, Lugo A, Jensen RL, Walker JM, Cloward TV. Simultaneous use of antidepressant and antihypertensive medications increases likelihood of diagnosis of obstructive sleep apnea syndrome. *Chest* 2004;**125**:1279–85.
48. Means MK, Lichstein KL, Edinger JD, Taylor DJ, Durrence HH, Husain AM, et al. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. *Sleep Breath* 2003;**7**:31–42.
49. Schwartz DJ, Kohler WC, Karatinos G. Symptoms of depression in individuals with obstructive sleep apnea may be amenable to treatment with continuous positive airway pressure. *Chest* 2005;**128**:1304–9.
50. Kawahara S, Akashiba T, Akahoshi T, Horie T. Nasal CPAP improves the quality of life and lessens the depressive symptoms in patients with obstructive sleep apnea syndrome. *Intern Med* 2005;**44**:422–7.
51. Munoz A, Mayoralas LR, Barbe F, Pericas J, Agusti AGN. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. *Eur Respir J* 2000;**15**:676–81.
52. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*; 2008:e45. doi:10.1371/journal.pmed.0050045.
53. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykityn IJ, Kay A, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;**165**:773–80.
54. Haensel A, Norman D, Natarajan L, Bardwell WA, Ancoli-Israel S, Dimsdale JE. Effect of a 2 week CPAP treatment on mood states in patients with obstructive sleep apnea: a double-blind trial. *Sleep Breath* 2007;**11**:239–44.
- *55. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*; 2006. CD001106.
56. Henke KG, Grady JJ, Kuna ST. Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypopnea syndrome. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2001;**163**:911–7.
57. Bardwell WA, Norman D, Ancoli-Israel S, Loreda JS, Lowery A, Lim W, et al. Effects of 2-week nocturnal oxygen supplementation and continuous positive airway pressure treatment on psychological symptoms in patients with obstructive sleep apnea: a randomized placebo-controlled study. *Behav Sleep Med* 2007;**5**:21–38.
58. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev*; 2006. CD004435.
59. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;**170**:656–64.
60. Naismith SL, Winter VR, Hickie IB, Cistulli PA. Effect of oral appliance therapy on neurobehavioral functioning in obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med* 2005;**1**:374–80.
- *61. Katon W, Lin EHB, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007;**29**:147–55.
62. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005;**58**:175–89.
- *63. Rosenberg RS. Depression in the sleep center: are we treating the whole patient? *Sleep Med* 2003;**4**:269.
64. Simon GE, Katon WJ, Lin EHB, Rutter C, Manning WG, Von Korff M, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. *Arch Gen Psychiatry* 2007;**64**:65–72.
65. Unutzer J, Katon W, Callahan CM, Williams JW, Hunkeler E, Harpole L, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002;**288**:2836–45.
66. de Jonge P, Honig A, van Melle JP, Schene AH, Kuyper AM, Tulner D, et al. Nonresponse to treatment for depression following myocardial infarction: association with subsequent cardiac events. *Am J Psychiatry* 2007;**164**:1371–8.
67. Riemann D, Berger M, Voderholzer U. Sleep and depression – results from psychobiological studies: an overview. *Biol Psychol* 2001;**57**:67–103.
68. Winokur A, Gary KA, Rodner S, Rae-Red C, Fernando AT, Szuba MP. Depression, sleep physiology, and antidepressant drugs. *Depress Anxiety* 2001;**14**:19–28.
69. Smith SS, Dingwall K, Jorgenson G, Douglas J. Associations between the use of common medications and sleep architecture in patients with untreated obstructive sleep apnea. *J Clin Sleep Med* 2006;**2**:156–62.
70. Akashiba T, Kawahara S, Akahoshi T, Omori C, Saito O, Majima T, et al. Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. *Chest* 2002;**122**:861–5.
71. Wells RD, Freedland KE, Carney RM, Duntley SP, Stepanski EJ. Adherence, reports of benefits, and depression among patients treated with continuous positive airway pressure. *Psychosom Med* 2007;**69**:449–54.
72. Yue W, Hao W, Liu P, Liu T, Ni M, Guo Q. A case–control study on psychological symptoms in sleep apnea-hypopnea syndrome. *Can J Psychiatry* 2003;**48**:318–23.
73. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000;**85**:1151–8.
74. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 1997;**82**:1313–6.
75. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor- α antagonist. *J Clin Endocrinol Metab* 2004;**89**:4409–13.
76. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav Immun* 2007;**21**:374–83.
77. Jans LAW, Riedel WJ, Markus CR, Blokland A. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. *Mol Psychiatry* 2007;**12**:522–43.
78. Fenik P, Veasey SC. Pharmacological characterization of serotonergic receptor activity in the hypoglossal nucleus. *Am J Respir Crit Care Med* 2003;**167**:563–9.
79. Reimer MA, Flemons WW. Quality of life in sleep disorders. *Sleep Med Rev* 2003;**7**:335–49.
80. Mrazek DA, Smoller JW, de Leon J, Ginsberg DL. Incorporating pharmacogenetics into clinical practice: reality of a new tool in psychiatry. *CNS Spectr* Mar 2006;vol. 11(3):1–2.