ORIGINAL ARTICLE

Sleep disturbances, anxiety and depression in patients with oral lichen planus: a case–control study

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Abstract

Background The psychological factors and their association with chronic inflammatory disease, aren't well recognized, yet their importance in oral lichen planus is still debated.

Aims The aim of this study was to investigate the prevalence of sleep disturbances, anxiety, depression and their association in patient with oral lichen planus.

Materials and methods 50 patients with oral lichen planus vs. equal number of age and sex-matched healthy controls were enrolled. Questionnaires examining insomnia symptoms, excessive daytime sleepiness (Pittsburgh sleep quality index and Epworth aleepiness scale) depression and anxiety (The Hamilton rating scale for Depression and Anxiety) were used.

Results The patients with oral lichen planus had statistically higher scores in all items of the Pittsburgh sleep quality index, the Hamilton rating scale for depression and anxiety and Epworth sleepiness scale than the healthy controls. The median and inter-quartile range of the Pittsburgh sleep quality index was 5-2 and for the oral lichen planus patients and 4-2 for the healthy controls ($P < 0.011$). In the study group, a depressed mood and anxiety correlated positively with sleep disturbances. The Pearson correlations were 0.76 for Pittsburgh sleep quality Index vs. Hamilton rating scale for depression ($P < 0.001$) and 0.77 for Pittsburgh sleep quality Index vs. Hamilton rating scale for anxiety ($P < 0.001$).

Discussion Oral lichen planus patients report a greater degree of sleep problems, depressed mood and anxiety as compared with controls.

Conclusion We suggest to screen sleep disturbances in patients with oral lichen planus because they could be considered a prodromal symptoms of mood disorders.

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Conflicts of interest

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Introduction

Lichen planus is a chronic inflammatory mucocutaneous disease that occurs in approximately 1–2% of the general adult population and commonly affects middle-aged females.[1] An immune-mediated pathogenesis is recognized, although the exact aetiology is unknown.[2–5] Oral lichen planus (OLP) can be considered along duration chronic disease of with dynamic evolution and frequent changes in clinical appearance, ranging from reticular, papular, plaque, cheratotic manifestations to atrophic and ulcerative (erosive) patterns.[6,7] Reticular OLP is often asymptomatic but the erosive forms of can cause symptoms ranging from oral burning sensation to severe pain, affecting the quality of life and mood.[8]

Some of the studies have shown that patients with OLP exhibit higher levels of anxiety, greater depression and increased vulnerability to psychic disorders, other studies included OLP as one of the psychosomatic diseases.[9–16] Other studies showed that no relevant connection between stress and/or psychological factors and OLP can be established.[17–19]

Sleep is vital to health and quality of life, whereas sleep disturbances (both insomnia and hypersomnolence) (SD) is associated with adverse health consequence.[20,21] Several studies highlight

that SD has been observed in a number of chronic inflammatory conditions such as autoimmune disease.[22,23] The association between SD, anxiety and depression has reported countless times, and it is related to common underlying pathophysiological mechanisms for sleep and mood regulation that make the individual vulnerable to both conditions.[24–27] The temporal relationship between SD and psychiatric problems may vary; often insomnia tends to precede or co-occur with mood disorders, whereas it tends to present at the same time or following onset of anxiety disorder.[28] Therefore, many authors consider SD as a risk factor for major depression and anxiety and highlight insomnia as a diagnostic symptom for depressive and anxiety disorders.[24,29–31]

To the best of our knowledge, this is the first study which analyse sleep complaints in patients with OLP, to determine its prevalence and association with depression and anxiety.

Materials and methods

This was a case–control clinical study carried out at the Oral Medicine Unit of the 'Federico II University of Naples'. Sixty-six cases and 56 controls were screened to participate between June 2011 and December 2011; 50 individuals with OLP and 50 healthy patients were included in the trial in accordance with the inclusion/exclusion criteria undergoing a simple randomization procedure with IBM SPSS software (version 19; IBM corporation, Armonk, NY, USA). Both groups were frequency-matched for sex, age and educational levels. All patients provided their written informed consent for the management of personal data before participating into the study. This study was approved by local Ethical Committee.

The inclusion criteria for OLP patients were: (i) either sex, aged 18 or older aged; (ii) the presence of bilateral clinical signs of symmetrical, reticular/papular patterned lesions; and (iii) the histological confirmation of clinical diagnosis via incisional biopsy exhibiting in a well-defined band like zone of cellular infiltration confined to the superficial part of the connective tissue, consisting mainly of lymphocytes, a sign of 'liquefaction degeneration' in the basal cell layer, and the absence of epithelial dysplasia. The exclusion criteria encompassed patients presenting with erosive/or atrophic and/or bullous lesions; patients with painful symptomatology, and subjects treated with oral and topical corticosteroids, or regularly treated with anxiolytic, antidepressants, anticonvulsants, or psychotropic drugs.

The inclusion criteria for healthy subjects were as follows: (i) either sex, aged 18 or older; (ii) the absence of oral mucosal lesions; (iii) no history of psychiatric disorder; and (iv) consultation exclusively for dental diseases. The exclusion criteria encompassed: (i) the patients with unstable medical conditions or debiliting pathologies, such as cancer, osteonecrosis, autoimmune blistering diseases; and (ii) the patients regularly treated with anxyolitic, antidepressants, anticonvulsants and/or psychotropic drugs.

Sociodemographic data, age, education, occupation and marital status were recorded for both OLP patients and healthy subjects. At admission, each subject underwent a medical anamnesis, a general medical examination, an intraoral and extraoral examination and psychiatric evaluation. The diagnosis of OLP was determined by clinical examination and confirmed by histological examination of an oral biopsy.

Upon admission, the OLP patients and healthy subjects were assessed in accordance with the following evaluation battery Scale: the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) for assessment of sleep and the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Rating Scale for Anxiety (HAM-A) for the evaluation of depression and anxiety.

All these scales were reviewed for completeness before collection and were administered in their Italian versions.

Assessment of sleep

The PSQI[32] is a standardized self-report questionnaire assessing sleep quality and disturbances.[32] This instrument comprises 19 items, generating 7 'component' scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Each item is scored from 0 to 3, with higher scores indicating poorer sleep or more frequent sleep problems. Items are combined to yield the seven components (scores ranging from 0 to 3), and the sum of the scores for these seven components yields 1 global score ranging from 0 to 21. Global scores above five distinguish poor sleepers from good sleepers with high sensitivity (90–99%) and specificity (84–87%).[32,33]

The ESS[34] is a simple, self-administered questionnaire, which measures subject's general level of daytime sleepiness. The instrument comprises eight items assessing the propensity for sleep in eight common situations. Subjects rate their likelihood of dozing in each situation on a scale of 0 (would never doze) to 3 (a high chance of dozing). The ESS score is the sum of the eight items. The ratings can be added together to form a total score of 24, with a cut-off value of >10 indicating excessive daytime sleepiness.[35]

Assessment of depression and anxiety

The HAM-D is a rating scale developed to measure the severity of depressive symptoms. HAM-D evaluates 21 items pertaining to the affective field. Scores can range from 0 to 54. A total score is computed reflecting the degree of symptom severity. A score >10 indicates impairment. Scores between 10 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression and scores over 24 indicate severe depression.[36–38] The HAM-A is a rating scale developed to measure the severity of anxiety symptoms. It consists of 14 items, each defined by a series of symptoms. Score can range from 0 to 56. A score of below 17 indicates mild severity, scores in the 18–24 range indi-

cate mild to moderate severity and from 25 to 30 indicate moderate to severe anxiety.[39,40]

Analysis

Descriptive statistics, including means, standard deviations, medians and interquartile range, were used to summarize all the variables. Considering the non-normality of the data analysed, the Mann–Whitney *U*-test was employed to test the significance of the study parameters between the OLP patients and controls. *P* values <0.05 were considered to reflect statistical significance.

A series of hierarchical multiple regression analyses was performed to test the importance of disease-related and psychosocial factors to sleep quality after checking for demographic factors. Each hierarchical regression analysis computed whether the variance explained by the specific set contributed significantly to the total variance in sleep quality after checking for the demographic set. A full model analysis was then computed with all the variables entered simultaneously into the model to determine the relative contributions of these variables to sleep quality.

Results

Table 1 summarizes the demographic and clinical parameters. There were 26 female patients (52%) and 24 male patients (48%).

PSQI reliability

Table 2 shows the reliability analysis of PSQI in OLP patients. The Cronbach α measure 0.62 indicated a good overall reliability of the scale. All components present an acceptable level of item-scale Pearson correlation. Item-scale correlation and Cronbach's alpha index were used to verify the internal consistency, item by item, and the global reliability of the PSQI in OLP patients and controls.

Sleep quality

The global and component scores for the PSQI were significantly different between cases and controls (Tables 1 and 3). Patients with OLP had higher mean PSQI scores, indicating a poorer sleep quality for these patients compared with the healthy controls. Twenty-one patients (42%) were poor sleepers with a PSQI global score of >5.

Patients with poor quality of sleep Among OLP patients, the clinical parameters of good (PSQI < 5) and poor (PSQI > 5) sleepers were compared. Depression ($P < 0.001$), anxiety ($P < 0.001$) and daytime sleepiness ($P < 0.001$) were found to be significantly different between the two groups (Table 4).

Dependence of sleep quality As shown in Table 5, depression (HAM-D), anxiety (HAM-A) and daytime sleepiness (ESS) correlated positively with sleep disturbances ($P < 0.001$). In 21 poor sleepers OLP patients, 18 showed mild depression (86%) and three no depression (14%), 21 showed mild anxiety.

Association with sleep quality The results of the hierarchical multiple regression analyses predicting sleep quality are shown in Table 6. Model 1 (the demographic model) tests the contribution of demographic variables to disturbed sleep. Model 2 (the depression model) tested the contribution of depressed mood to poor sleep quality after controlling for the demographic variables. Model 3 (the anxiety model) tested the contribution of anxiety mood to poor sleep after controlling for the demographic variables. Model 4 (the daytime sleepiness model) tested the contribution of daytime sleepiness to poor sleep quality of sleep after controlling for the demographic variables. Models 1–4 are the results of hierarchical regression analyses, which are usually undertaken in research to determine the importance of predictor variables once the other predictor variables have already been entered into the equation. Model 5 is the standard

Table 1 Demographic and clinical characteristics of OLP patients and control subjects

Demographic variables	OLP patients	Control patients	*P*-value
	Mean ± SD	Mean ± SD	
Age	55.020 ± 7.238	53.200 ± 8.569	0.254
Years of education	8.780 ± 2.971	9.320 ± 2.910	0.360
Gender	Male:Female 24:26	Male:Female 24:26	–
Marital status	Married:Unmarried 42:8	Married:Unmarried 42:8	–
Full-time job	Yes:No 24:26	Yes:No 11:39	–
Clinical parameters	**Median–IQR**	**Median–IQR**	***P*-value**
PSQI	5.0–2.0	4.0–2.0	<0.011*
HAM-D	7.0–3.0	5.0–2.0	<0.001**
HAM-A	7.5–3.0	5.0–3.0	<0.001**
EPS	3.0–1.0	3.0–1.0	0.168

IQR is the interquartile range. The significance difference between medians was measured by Mann–Whitney *U*-test.
*Moderately significant $0.01 < P \leq 0.05$, **strongly significant $P \leq 0.01$.

Table 2 Reliability analysis of PSQI scale in OLP patients and control subjects

PSQI components	Item-scale correlation ρ	
	OLP cases	Control cases
Subjective sleep quality	0.42	0.51
Sleep latency	0.29	0.32
Sleep duration	0.63	0.43
Habitual sleep efficiency	0.59	0.36
Sleep disturbances	0.16*	0.03*
Use of sleep medications	–	0.61
Daytime dysfunction	0.13*	0.17*
Cronbach Alpha	0.62	0.65

*Poor correlation between a single item and the global scale (ρ < 0.3).

regression analysis where all of the variables were entered simultaneously into the model to assess the relative contributions of these variables to sleep quality. This model takes into account the interrelations between the predictor variables as well as the effects of the predictor variables on the outcome variable (PSQI).

The first model testing the contributions of demographic variables to sleep quality was not found to be statistically significant (R^2 = 6.3%, P = 0.560). The addition of depression (model 2) and anxiety (model 3) resulted in a significant increase in the R^2 value (ΔR^2 = 55.1%, P = 0.001 for depression, ΔR^2 = 57.2%, P = 0.001 for anxiety). The final full model (the standard multiple regression analysis) in which all of the variables were entered simultaneously could explain 75% of the variance in sleep quality. The analysis of dependence reported in Table 5 highlights a very strong correlation between the PSQI and the Epworth Sleepiness Scale (ESS). This result is consistent with the similar nature of the two scales and therefore the ESS can be considered as a proxy variable of PSQI.

Discussion

OLP etiopathogenesis is complex, with genetic, environmental and lifestyle factors reported.[41,42]

In previous studies, in patients with erosive OLP, stress, depression and anxiety were all correlated with severe, symptomatic oral involvement therefore depression and anxiety were considered be secondary factors and as consequence of pain; for this reason we selected only asymptomatic cheratotic forms of OLP.

In this study, the prevalence of SD in patients with OLP was 42%. PSQI global and all of the component scores were significantly higher for patients with OLP than healthy controls. This clearly depicts the poorer sleep quality of OLP patients when compared with healthy subjects. Patients with PSQI >5 had significantly higher levels of anxiety and depression: 18 patients

Table 3 Comparison of components of PSQI in OLP patients and control subjects

PSQI components	OLP cases			Control cases			*P*-value
	Median	IQR	Range	Median	IQR	Range	
Subjective sleep quality	1	0	[0–2]	1	0	[0–2]	0.105
Sleep latency	1	1	[0–3]	0	1	[0–2]	0.315
Sleep duration	1	0	[0–3]	1	0	[0–2]	0.866
Habitual sleep efficiency	1	1	[0–2]	1	1	[0–3]	0.128
Sleep disturbances	1	0	[0–6]	0	1	[0–3]	0.008**
Use of sleep medications	0	0	[0–0]	0	0	[0–3]	0.082
Daytime dysfunction	0	1	[0–3]	0	1	[0–4]	0.795

IQR is the interquartile range.
The significance difference between medians was measured by Mann–Whitney *U*-test.
**strongly significant $P \leq 0.01$.

Table 4 Comparison between good and poor sleepers for OLP patients

PSQI components	PSQI ≤ 5 (*n* = 29)			PSQI > 5 (*n* = 21)			*P*-value
	Median	IQR	Range	Median	IQR	Range	
Depression (HAM-D)	6.0	2.5	[2–10]	9.0	3.0	[4–18]	<0.001**
Anxiety (HAM-A)	6.0	2.5	[2–9]	10.5	4.0	[4–20]	<0.001**
Daytime sleepiness (ESS)	3.0	1.0	[2–4]	4.0	2.0	[3–14]	<0.001**

IQR is the interquartile range.
The significance difference between medians was measured by Mann–Whitney *U*-test.
**strongly significant $P \leq 0.01$.

Table 5 Dependence of sleep quality with clinical parameters and demographic characteristics a clinical for OLP patients

	Pearson ρ coefficient		*P*-value
Clinical parameters			
Depression (HAM-D)	0.76		<0.001**
Anxiety (HAM-A)	0.77		<0.001**
Daytime sleepiness (ESS)	0.76		<0.001**
Demographic characteristics			
Age	0.21		0.036*
Years of education	−0.15		0.144
	Median–IQR	Median–IQR	
Gender	Male 5.5–2.5	Female 4.5–3.0	0.258
Marital status	Yes 5.0–3.0	Not 6.5–3.0	0.401

IQR is the interquartile range.
For numerical variables *P*-values were obtained by Pearson correlation test. For qualitative characteristics *P*-values were obtained by Mann–Whitney test.
*Moderately significant $0.01 < P \leq 0.05$. **strongly significant $P \leq 0.01$.

(86%) showed mild depression (HAM-D median 9–IQR 3) and all patients present mild anxiety (HAM-A median 10.5–IQR 4). Interestingly, none of them were taking antidepressants and this could be due to the probable underestimation of depression and anxiety in disease like OLP. In our study, the association between depression ($P < 0.001$), anxiety ($P < 0.001$), daytime sleepiness ($P < 0.01$) and sleep quality in OLP patients, which was evident and significant on bivariate analysis, remains significant in standard multiple regression analyses.

In previous studies, SD often occurs in conjunction with psychiatric disorders, most notably depression and anxiety, both of which have SD as a diagnostic criterion.[43–45] There are a number of longitudinal studies demonstrating an increased risk of new-onset psychopathology over time in individuals with SD at baseline.[46,47] In cases of remitted depression, SD often is a residual problem that confers increased risk for relapse.[48,49] In case where SD do resolve it often occurs as prodromal symptom prior to relapse.[50]

OLP pathogenesis remains highly debated but it is generally accepted an underlying immune-mediated mechanism. An unknown antigen could be processed and presented by resident presenting antigen cells and keratinocytes inducing an MHC class II, T-cell-mediated immunologic response. Activated T cells expressed adhesion molecules (VLAs, VCAMs, ICAMs) together with maturation markers (CD25, CD71, CD45RO) producing Th1 cytokines (IL-2 and IFN-gamma).[51] CD4+ helper T cells via Th1 cytokines can activate CD8+ cytotoxic T cells to trigger basal keratinocytes apoptosis via TNF-α.[52] TNF-α expression can improve the activation of NF-kB in subepithelial T cells leading to increase the expression of other inflammatory cytokines including IL-8 and IL-6.[53,54] It has been demonstrated that OLP patients show also systemic impaired T cells response: the percentage and number of peripheral blood CD4+, CD45RA+ T lymphocytes are increased together with serum levels of TNF-α, IL-6 and IL-10.[1,55] In this context of inflammation, cytokines can access the central nervous system and interact with the cytokines network of the brain with deep influence on the function.[56]

Alterations in immune function have been found in depressed patients including early reports of immune suppression followed by evidence of increased inflammatory activity (e.g. increased

Table 6 Multiple linear regression model predicting sleep quality in OLP patients

Predictors	Model 1		Model 2		Model 3		Model 4		Model 5	
	Beta (SE)	*P*-value	Beta (SE)	*P*-value	Beta (SE)	*P*-value	Beta (SE)	*P*-value	Beta (SE)	*P*-value
Age	0.04 (0.05)	0.449	0.03 (0.03)	0.393	0.03 (0.03)	0.435	0.03 (0.03)	0.273	0.03 (0.03)	0.301
Years of education	0.02 (0.13)	0.884	0.13 (0.08)	0.120	0.07 (0.08)	0.405	0.08 (0.07)	0.290	0.10 (0.07)	0.162
Gender: Female	−0.48 (0.74)	0.519	−0.37 (0.48)	0.441	−0.28 (0.47)	0.555	−0.32 (0.44)	0.462	−0.30 (0.40)	0.459
Marital status: Married	−1.36 (1.01)	0.201	−1.15 (0.68)	0.099+	−1.18 (0.66)	0.081+	−1.11 (0.61)	0.081+	−1.10 (0.57)	0.058+
Depression (HAM-D)			0.75 (0.09)	<0.001**					0.19 (0.16)	0.233
Anxiety (HAM-A)					0.61 (0.07)	<0.001**			0.19 (0.13)	0.157
Daytime sleepiness (ESS)							1.73 (0.19)	<0.001**	1.01 (0.28)	<0.001**
R^2 (%)	6.3	0.560	61.4	<0.001**	63.5	<0.001**	68.1	<0.001**	74.7	<0.001**
R^2 change (%)			55.1	<0.001**	57.2	<0.001**	61.8	<0.001**	68.4	<0.001+

SE are the standard errors of beta estimates. *P*-values were obtained by hypothesis test on regression coefficients. + Suggestive of significance $0.05 < P \leq 0.10$.
*Moderately significant $0.01 < P \leq 0.05$. **strongly significant $P \leq 0.01$.

circulating levels of inflammatory markers as pro-inflammatory cytokines, including interleukin-1,IL-6 and tumour necrosis factor, TNF-α). This evidence has led to the hypothesis that cytokines and inflammatory factors may be involved in the pathophysiology of neuropsychiatric disorders such as depression.[56–58] Several studies revealed that pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α are implicated in the regulation of sleep and that sleep is a strong regulator of immunological processes.[59,60] Sleep disturbance may enhance pro-inflammatory cytokine production, e.g. TNF-α and IL-6, leading to suggestions of bidirectional communication between the central nervous and immune system which is mediated by shared signals (neurotransmitters, hormones and cytokines).[61–65] In OLP patients, saliva and serum IL-6 and TNF-α concentrations were suggested to be useful in monitoring disease activity status and therapeutic response, with a reduction associated with significant subjective improvement in discomfort symptoms following treatment.[55,66,67] This context suggests that psychobiological mechanisms may contribute to OLP pathogenesis and that psychiatric comorbidity may enhance OLP immunological reactivity.

In our study, OLP patients with SD showed levels of anxiety and depression higher than good sleepers. According to the literature,[68–70] we suppose that SD are the starting point for the initiation of anxiety and depression already considered risk factors for OLP and suggested the importance of screening for SD in OLP patients. PSQI and ESS are high sensitivity tests, easy to perform and it could be useful to screen SD in OLP patients and we suggest to investigate via questionnaires, the presence of anxiety and depression only in patients with PSQI> 5.

Limitation

Our study sample included many patients over 40 years of age for whom SD is a common complaint regardless of physical conditions, the study was cross-sectional and we could not established the cause–effect relationship of the psychic aspects of the individual and the oral findings.

Conclusions

This study has confirmed the comorbidity of sleep disturbances, anxiety and depression in a sample of asymptomatic and cheratotic OLP. Our results emphasize the importance of assessing of sleep variables in clinical evaluation and possibly, in treatment. Further investigations are needed to evaluate the relationships among SD, mood disorders and the chronic course of the different clinical variance of OLP.

References

1 Sugerman PB, Savage NW. Oral lichen planus: causes, diagnosis and management. *Aust Dent J* 2002; **47**: 290–297. Review.
2 Porter SR, Kirby A, Olsen I, Barrett W. Immunologic aspects of dermal and oral lichen planus: a review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **83**: 358–366. Review.
3 Rodríguez-Núñez I, Blanco-Carrión A, García AG, Rey JG. Peripheral T-cell subsets in patients with reticular and atrophic-erosive oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 180–188.
4 Eisen D, Carrozzo M, Bagan Sebastian JV, Thongprasom K. Number V Oral lichen planus: clinical features and management. *Oral Dis* 2005; **11**: 338–349. Review.
5 Bagán-Sebastián JV, Milián-Masanet MA, Peñarrocha-Diago M, Jiménez Y. A clinical study of 205 patients with oral lichen planus. *J Oral Maxillofac Surg* 1992; **50**: 116–118.
6 Scully C, el-Kom M. Lichen planus: review and update on pathogenesis. *J Oral Pathol* 1985; **14**: 431–458. Review.
7 Sugerman PB, Savage NW, Walsh LJ *et al.* The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med* 2002; **134**: 350–365.
8 Lundqvist EN, Wahlin YB, Bergdahl M, Bergdahl J. Psychological health in patients with genital and oral erosive lichen planus. *J Eur Acad Dermatol Venereol* 2006; **20**: 661–666.
9 Preda EG, Pasetti P, Caggiula S, Nidoli G, Boggio E, Azzi R. Oral pathology of pscyhosomatic origin. review of the literature. *Dent Cadmos* 1990; **31**: 66–72.
10 Bergdahl J, Ostman PO, Anneroth G, Perris H, Skoglund A. Psychologic aspects of patients with oral lichenoid reactions. *Acta Odontol Scand* 1995; **53**: 236–241.
11 Hampf BG, Malmström MJ, Aalberg VA, Hannula JA, Vikkula J. Psychiatric disturbance in patients with oral lichen planus. *Oral Surg Oral Med Oral Pathol* 1987; **63**: 429–432.
12 Rojo-Moreno JL, Bagán JV, Rojo-Moreno J, Donat JS, Milián MA, Jiménez Y. Psychologic factors and oral lichen planus. a psychometric evaluation of 100 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; **86**: 687–691.
13 Soto Araya M, Rojas Alcayaga G, Esguep A. Association between psychological disorders and the presence of Oral lichen planus, Burning mouth syndrome and Recurrent aphthous stomatitis. *Med Oral* 2004; **9**: 1–7.
14 Koray M, Dülger O, Ak G *et al.* The evaluation of anxiety and salivary cortisol levels in patients with oral lichen planus. *Oral Dis* 2003; **96**: 298–301.
15 Ivanovski K, Nakova M, Warburton G *et al.* Psychological profile in oral lichen planus. *J Clin Periodontol* 2005; **32**: 1034–1040.
16 Girardi C, Luz C, Cherubini K, de Figueiredo MA, Nunes ML, Salum FG. Salivary cortisol and dehydroepiandrosterone (DHEA) levels, psychological factors in patients with oral lichen planus. *Arch Oral Biol* 2011; **56**: 864–868.
17 Macleod RI. Psychological factors in oral lichen planus. *Br Dent J* 1992; **173**: 88.
18 Humphris G, Field EA. Psychological factors in oral lichen planus. *Br Dent J* 1992; **173**: 331.
19 Allen CM, Beck FM, Rossie KM, Kaul TJ. Relation of stress and anxiety to oral lichen planus. *Oral Surg Oral Med Oral Pathol* 1986; **61**: 44–46.
20 Parish JM. Sleep-related problems in common medical conditions. *Chest* 2009; **135**: 563–572.
21 Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med* 2007; **15**: 7–10. Review.
22 Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev* 2008; **12**: 211–228.
23 Walsh JK, Muehlbach MJ, Lauter SA, Hilliker NA, Schweitzer PK. Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. *J Rheumatol* 1996; **23**: 245–252.
24 Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996; **15**: 411–418.
25 Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med* 1998; **158**: 1099–1107.
26 Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep* 2007; **30**: 873–880.

27 Richardson GS. Human physiological models of insomnia. *Sleep Med* 2007; **4**: S9–S14.
28 Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res* 2003; **37**: 9–15.
29 Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: a prospective perspective. *Am J Psychiatry* 2000; **157**: 81–88.
30 Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. *Am J Epidemiol* 1997; **146**: 105–114.
31 Taylor DJ. Insomnia and depression. *Sleep* 2008; **31**: 447–448.
32 Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193–213.
33 Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. *J Psychosom Res* 1998; **45**: 5–13.
34 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**: 540–545.
35 Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep* 1992; **154**: 376–381.
36 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56–62.
37 Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; **6**: 278–296.
38 Morriss R, Leese M, Chatwin J, Baldwin D. Inter-rater reliability of the Hamilton Depression Rating Scale as a diagnostic and outcome measure of depression in primary care. *J Affect Disord* 2008; **111**: 204–213.
39 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959; **32**: 50–55.
40 Hamilton M. Development of a Rating Scale for Primary Depressive Illness. *Br J Soc Clin Psychol* 1967; **6**: 278–296.
41 Shah B, Ashok L, Sujatha GP. Evaluation of salivary cortisol and psychological factors in patients with oral lichen planus. *Indian J Dent Res* 2009; **20**: 288–292.
42 Vallejo MJ, Huerta G, Cerero R, Seoane JM. Anxiety and depression as risk factors for oral lichen planus. *Dermatology* 2001; **203**: 303–307.
43 Association AP. Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR). 4th ed. Text Revision ed. Washington, DC: American Psychiatric Association; 2000.
44 Stepanski EJ, Rybarczyk B. Emerging research on the treatment and etiology of secondary or comorbid insomnia. *Sleep Med Rev* 2006; **10**: 7–18.
45 McCrae CS, Lichstein KL. Secondary insomnia: diagnostic challenges and intervention opportunities. *Sleep Med Rev* 2001; **5**: 47–61.
46 Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression? *J Affect Disord* 2003; **76**: 255–259.
47 Morawetz D. Depression and insomnia. *Aust Fam Physician* 2000; **29**: 1016.
48 Karp JF, Buysse DJ, Houck PR, Cherry C, Kupfer DJ, Frank E. Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. *Am J Psychiatry* 2004; **161**: 1877–1884.
49 Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG. Remission and relapse in major depression: a two-year prospective follow-up study. *Psychol Med* 1995; **25**: 1161–1170.
50 Perlis ML, Giles DE, Buysse DJ, Tu X, Kupfer DJ. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *J Affect Disord* 1997; **42**: 209–212.
51 Prolo P, Chiappelli F, Cajulis E *et al.* Psychoneuroimmunology in oral biology and medicine: the model of oral lichen planus. *Ann N Y Acad Sci* 2002; **966**: 429–440.
52 Roopashree MR, Gondhalekar RV, Shashikanth MC, George J, Thippeswamy SH, Shukla A. Pathogenesis of oral lichen planus–a review. *J Oral Pathol Med* 2010; **39**: 729–734.
53 Zhang Y, Lin M, Zhang S *et al.* NF-kappaB-dependent cytokines in saliva and serum from patients with oral lichen planus: a study in an ethnic Chinese population. *Cytokine* 2008; **41**: 144–149.
54 Nibali L, Fedele S, D'Aiuto F, Donos N. Interleukin-6 in oral diseases: a review. *Oral Dis* 2012; **18**: 236–243.
55 Pekiner FN, Demirel GY, Borahan MO, Ozbayrak S. Cytokine profiles in serum of patients with oral lichen planus. *Cytokine* 2012; **60**: 701–706.
56 Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 2011; **130**: 226–238.
57 Motivala SJ. Sleep and inflammation: psychoneuroimmunology in the context of cardiovascular disease. *Ann Behav Med* 2011; **42**: 141–152.
58 Evans DL, Charney DS, Lewis L *et al.* Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005; **58**: 175–189.
59 Anisman H, Hayley S. Inflammatory factors contribute to depression and its comorbid conditions. *Sci Signal* 2012; **5**: 244.
60 Opp MR. Cytokines and sleep. *Sleep Med Rev* 2005; **9**: 355–364.
61 Zorrilla EP, Luborsky L, McKay JR *et al.* The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav Immun* 2001; **15**: 199–226.
62 Miller AH. Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. *Brain Behav Immun* 2009; **23**: 149–158.
63 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 2009; **65**: 732–741.
64 Howren MB, Suls J, Martin R. Depressive symptomatology, rather than neuroticism, predicts inflated physical symptom reports in community-residing women. *Psychosom Med* 2009; **71**: 951–957.
65 Dowlati Y, Herrmann N, Swardfager W *et al.* A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010; **67**: 446–457.
66 Chiappelli F, Kung MA, Nguyen P, Villanueva P, Farhadian EA, Eversole LR. Cellular immune correlates of clinical severity in oral lichen planus: preliminary association with mood states. *Oral Dis* 1997; **3**: 64–70.
67 Prolo P, Chiappelli F, Fiorucci A, Dovio A, Sartori ML, Angeli A. Psychoneuroimmunology: new avenues of research for the twenty-first century. *Ann N Y Acad Sci* 2002; **966**: 400–408.
68 Gulec M, Selvi Y, Boysan M, Aydin A, Besiroglu L, Agargun MY. Ongoing or re-emerging subjective insomnia symptoms after full/partial remission or recovery of major depressive disorder mainly with the selective serotonin reuptake inhibitors and risk of relapse or recurrence: a 52-week follow-up study. *J Affect Disord* 2011; **134**: 257–265.
69 Conradi HJ, Ormel J, de Jonge P. Symptom profiles of DSM-IV-defined remission, recovery, relapse, and recurrence of depression: the role of the core symptoms. *Depress Anxiety* 2012; **29**: 638–645.
70 Naismith SL, Rogers NL, Lewis SJ *et al.* Sleep disturbance relates to neuropsychological functioning in late-life depression. *J Affect Disord* 2011; **132**: 139–145.