

The association between burning mouth syndrome and sleep disturbance: A case–control multicentre study

D Adamo¹  | A Sardella² | E Varoni² | C Lajolo³ | M Biasotto⁴ | G Ottaviani⁴ | P Vescovi⁵ | T Simonazzi⁵ | M Pentenero⁶  | M Ardore⁶ | F Spadari⁷ | G Bombeccari⁷ | L Montebugnoli⁸ | DB Gissi⁸ | G Campisi⁹ | V Panzarella⁹ | M Carbone¹⁰ | L Valpreda¹⁰ | M Giuliani¹¹ | M Aria¹² | L Lo Muzio^{11†} | MD Mignogna^{1†}

¹Oral Medicine Complex Unit, Head & Neck Clinical Section, Department of Neurosciences, Reproductive and Odontostomatological Sciences, "Federico II" University of Naples, Naples, Italy

²Unit of Oral Pathology, Oral Medicine and Gerodontology, Department of Biomedical, Surgical and Dental Sciences, AO San Paolo Hospital of Milan, University of Milan, Milan, Italy

³Oral Pathology and Medicine, School of Dentistry, Catholic University of Rome, Rome, Italy

⁴Oral Medicine and Pathology Unit, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy

⁵Unit of Oral Pathology, Medicine and Laser Surgery, Department of Biomedical, Biotechnological and Translational Sciences, University of Parma, Parma, Italy

⁶Oral Medicine and Oral Oncology Unit, Department of Oncology, University of Turin, Turin, Italy

⁷Unit of Oral Pathology and Medicine, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Ospedale Maggiore Policlinico IRCCS Ca' Granda Foundation, Milan, Italy

⁸Unit of Oral Pathology and Medicine, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

⁹Department of Surgical, Oncological, and Oral Sciences, Sector of Oral Medicine "Valerio Margiotta", University of Palermo, Palermo, Italy

¹⁰Oral Medicine Section, Department of Surgical Sciences, CIR Dental School, University of Turin, Turin, Italy

¹¹Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

¹²Laboratory and Research Group STAD Statistics, Technology, Data Analysis Department of Economics and Statistics, "Federico II University of Naples", Naples, Italy

Correspondence

Daniela Adamo, Oral Medicine Complex Unit, Head & Neck Clinical Section, Department of Neurosciences, Reproductive and Odontostomatological Sciences, "Federico II" University of Naples, Naples, Italy.
Email: danielaadamo.it@gmail.com

Funding information

The work was supported by the Department of Neurosciences, Reproductive and Odontostomatological Sciences, Oral Medicine Unit, of the "Federico II University of Naples," Italy.

Objectives: To investigate the quality of sleep and the psychological profiles of a large cohort of Italian patients with burning mouth syndrome (BMS) and to clarify the relationships between these variables and pain.

Methods: In this case–control study, 200 patients with BMS vs an equal number of age- and sex-matched healthy controls, recruited in 10 universities, were enrolled. The Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), Numeric Pain Intensity Scale (NRS) and Total Pain Rating Index (T-PRI) were administered. Descriptive statistics, including the Mann–Whitney U test and hierarchical multiple linear regression analysis, were used.

Results: Poor sleep quality (PSQI ≥ 5) was present in 78.8% (160) patients with BMS. BMS patients had statistically higher scores in all items of the PSQI and ESS than the healthy controls ($p < .001$). A depressed mood and anxiety correlated positively with sleep disturbance. The Pearson correlations were 0.570 for the PSQI vs HAM-D ($p < .001$) and 0.549 for the PSQI vs HAM-A ($p < .001$). Pain intensity (NRS) poorly

[†]The last two authors contributed equally to the paper.

correlated to sleep quality; the Pearson correlation was 0.162 for the PSQI vs NRS ($p = .021$).

Conclusions: The BMS patients showed a poor sleep quality, anxiety and depression, as compared with the controls, highlighting the relationships between oral burning, sleep and mood.

KEYWORDS

anxiety, burning, insomnia symptoms, mood disorders, pain, sleep

1 | INTRODUCTION

Burning mouth syndrome (BMS) is an idiopathic, chronic orofacial pain disorder in which the patient presents with the sensation of burning and pain in the oral mucosa (Grushka, Epstein, & Gorsky, 2002), although this is not associated with clinical mucosal alterations and laboratory tests (Scala, Checchi, Montevecchi, Marini, & Giamberardino, 2003; Sun et al., 2013).

The prevalence is 0.7%–4.6%, with middle-aged women after the menopause more commonly afflicted (Charleston, 2013; Spanemberg, Rodríguez de Rivera Campillo, Salas, & López López, 2014).

The oral discomforts may be variable in intensity and cause with, in severe cases, a serious impairment in the patient's quality of life. The symptoms of BMS usually continue for a minimum of 4–6 months, remaining consistent and bilateral, only alleviated at meal times; pain tends to increase in the late afternoon or in the evening (Scala et al., 2003).

An oral and peri-oral burning sensation is the most frequently reported symptom, with patients often describing the pain as scalding, tingling, or numbing (Grushka, Epstein, & Gorsky, 2003). Other subjective oral symptoms, such as dysgeusia, xerostomia, sialorrhea, and intra-oral roughness or granularity sensation, have been reported (Adamo et al., 2015). Commonly, there are no obvious provoking factors, although in some cases BMS patients have reported antecedent dental procedures, the initiation of new medical treatment, or stressful life events (Frutos, Rodríguez, Miralles-Jorda, & Machuca, 2002).

There is no consensus concerning the etiopathogenesis of BMS with conflicting opinions reported in the literature. Some research studies focusing on the peripheral alterations indicate that BMS could result from a neuropathic trigeminal condition (Jääskeläinen & Woda, 2017). In other studies, a central brain dysfunction, such as an impaired endogenous dopamine system, has been identified (Hagelberg et al., 2004). In addition, several studies have shown a high prevalence of psychiatric disorders or of psychological problems (Abetz & Savage, 2009; Maina, Albert, Gandolfo, Vitalucci, & Bogetto, 2005; Schiavone et al., 2012) and sleep disturbance (SD) in BMS patients (Adamo et al., 2013; Lopez-Jornet et al., 2015).

Sleep is increasingly being recognized as essential to maintain mental and physical health with poor sleep acknowledged to contribute to a reduced quality of life.

Sleep disturbance includes those disease conditions in which sleeping patterns are disturbed with a significant and negative impact on patient health. SD is frequently reported in the general population, with a greater incidence among women and people with psychiatric diseases (Morin et al., 2011; Roy & Smith, 2010). Insomnia is the most common SD. According to DSM-5, a diagnosis of insomnia is determined according to the following criteria: (i) dissatisfaction with sleep quantity or quality, including difficulty initiating and maintaining sleep and waking up in the early morning; (ii) an SD that causes a serious reduction in normal daytime activity (e.g., cognitive impairment, mood disturbance, impaired work function); (iii) an SD that arises at least three nights per week and has been occurring for at least 3 months; and (iv) a sleep impairment that arises even if there is sufficient opportunity for sleep [American Psychiatric Association (APA), 2013]. Estimates of the prevalence of insomnia differ according to the criterion under consideration. In general, 35%–50% of the general population report that they are affected by one or more of the symptoms of insomnia (Walsh, Salkeld, Knowles, Tasker, & Hunneyball, 2010).

Sleep disturbance is a complex phenomenon and the subject of much debate. Some researchers consider SD to be a clinical condition in itself but for others it is only a symptom of another mental disorder (Billiard & Bentley, 2004; Lee et al., 2013; Ohayon, 2007). Indeed, patients with SD, frequently, present with other chronic illnesses such as hypertension, diabetes, obesity, depression, and anxiety. Moreover, SD has a frequent association with somatic and pain symptoms (Chung & Tso, 2010).

Sleep disturbance, somatic chronic pain, and mood disorders are closely connected (Finan & Smith, 2013; Ohayon, 2009). Sleep and pain have a reciprocal relationship and longitudinal population studies have highlighted that SD can provoke an increased sensitivity to pain leading to an exacerbation of other symptoms. Furthermore, patients affected by chronic pain suffer from an inadequate quality of sleep including sleep latency, sleep inefficiency, and awakenings after the onset of sleep (de Tommaso et al., 2014).

Various research studies have suggested that between 67% and 88% of patients suffering from chronic pain disorders report sleep complaints (Morin et al., 2011; Smith & Haythornthwaite, 2004) and that approximately 50% of people affected by insomnia present chronic pain (Taylor et al., 2007).

The association of SD with a negative mood, particularly with anxiety and depression, has, frequently, been described in relation

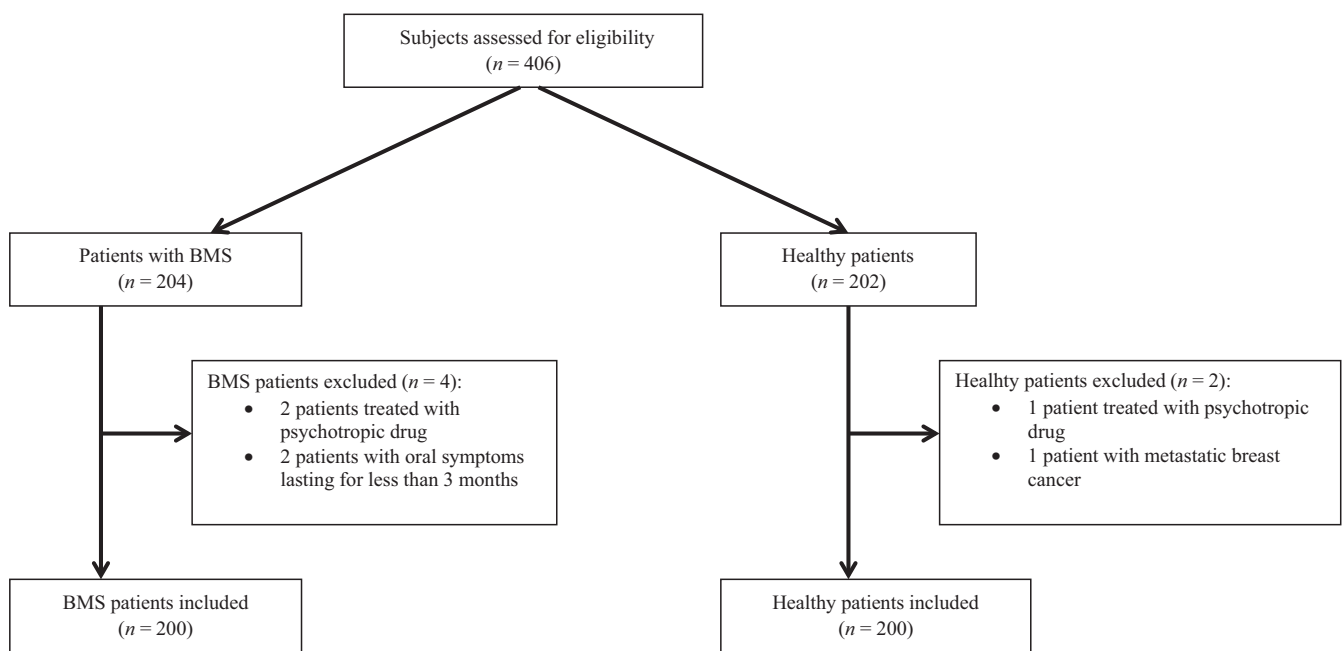


FIGURE 1 Flow chart of the study

to common underlying pathophysiological mechanisms (Benca & Peterson, 2008; Cox & Olatunji, 2016; Rumble, White, & Benca, 2015). Indeed, depression and anxiety are regarded by many clinicians as risk factors for SD (Smagula, Stone, Fabio, & Cauley, 2016) while poor sleep, in turn, may be a precursor of mood disorders that subsequently arise (Lee et al., 2013; Neckelmann, Mykletun, & Dahl, 2007). Moreover, persistent insomnia is frequently reported by depressed patients, contributing to non-remission (Ohayon, 2007).

Sleep disturbance in BMS is poorly documented, but recently there has been increasing attention devoted to the topic; a few single center studies have evaluated the comorbidity between mood and sleep impairments in BMS (Adamo et al., 2013; Chainani-Wu, Madden, & Silverman, 2011; Lopez-Jornet et al., 2015).

The aims of the present multicenter study have been to analyze the prevalence of insomnia, daytime sleepiness, anxiety, and depression in an extensive cohort of Italian patients with BMS, compared to a control group of healthy individuals, and to investigate the relationships between these variables and pain to have a greater awareness of the importance of SD in the management and therapy of BMS patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This observational and descriptive case-control study was carried out between March 2014 and January 2015. Ten Italian University Oral Medicine Units across the country participated in the study. It is compliant with the ethical principles of the World Medical Association Declaration of Helsinki. All patients and controls gave their written informed consent. The Ethics Committee of the Federico II University of Naples approved the study (No. 222/14).

The reporting of data followed the guidelines of the STROBE statement.

2.2 | Participants

Twenty BMS patients and 20 healthy control subjects were recruited and randomly selected with IBM SPSS software (version 19; IBM corporation Armonk NY, USA) in 10 Oral Medicine Units of different Italian Universities (seven northern, one central and two southern universities) making a total of 200 BMS patients and 200 healthy control subjects.

The identification of these two groups was carried out taking into account the inclusion/exclusion criteria reported below (Figure 1).

The BMS group inclusion criteria were, in accordance with the International Classification of Headaches (the International Classification of Headache Disorders: 3rd edition, 2013):

1. Male or female, aged at least 18.
2. Continuous symptoms of oral burning or pain persisting for at least 2 hr/day, lasting for longer than 3 months, with no paroxysm and not following any unilateral nerve trajectory.
3. No clinical mucosal alterations.
4. Normal blood test findings (including blood count, blood glucose, serum iron, ferritin and transferrin, folic acid, and vit B-12 levels).
5. A body mass index (BMI) less than 30.

The BMS group exclusion criteria were as follows:

1. Patients with diseases that could be recognized as a causative factor of BMS.
2. Patients in treatment with anxiolytics, antidepressants, anticonvulsants and/or psychotropic drugs.

3. A BMI greater than 30.
4. History or diagnosis of obstructive sleep apnea (OSA).
5. Heavy smokers (≥ 20 cigarettes/day) and heavy drinkers (14 units/week).

The control group included a randomized cluster of patients presenting at the University exclusively for dental care, during the study period.

The healthy subject group inclusion criteria were as follows:

1. Male or female, aged at least 18.
2. No oral mucosal lesions.
3. No record of psychiatric illness.
4. A BMI less than 30.

The exclusion criteria encompassed:

1. Patients with debilitating medical conditions.
2. Patients in treatment with anxiolytics, antidepressants, anticonvulsants, and/or psychotropic drugs.
3. A BMI greater than 30.
4. History or diagnosis of obstructive sleep apnea (OSA).
5. Heavy smokers (≥ 20 cigarettes/day) and heavy drinkers (14 units/week).

Body mass index in kg/m^2 was calculated from self-reported weight and height. Short sleep duration and impaired sleep quality are positively associated with a BMI greater than 30. Therefore, we decided to exclude these subjects from the study (Patel & Hu, 2008).

Data relating to sociodemographic factors were analyzed for each group.

During hospitalization, each subject underwent a careful medical anamnesis, a general medical examination, an intra-oral and extra-oral examination, laboratory tests, and ENT (ear, nose and throat) and psychiatric evaluation.

The data collection was performed by standardized clinical interview, conducted by an individual interviewer at each University.

The patients responded to the following evaluation battery scale:

1. The Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) for the evaluation of quality of sleep and daytime sleepiness.
2. The Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A) for the evaluation of depression and anxiety.
3. The Numeric Pain Intensity Scale (NRS) and the Total Pain Rating Index (T-PRI) the NRS and T-PRI from the short form of the McGill Pain Questionnaire (SF-MPQ) for the assessment of discomfort, pain intensity, and quality.

All these scales were examined for completeness and were administered in their Italian version.

2.3 | Assessment of sleep

The PSQI is a standardized self-report questionnaire evaluating sleep quality and disturbance. It consists of 19 items, relating to seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, the use of sleep medication, and daytime dysfunction. For each domain, a direct score is assigned, ranging from 0 to 3 according to the degree of severity (a score of zero indicates no problem while three indicates a serious problem). The scores are added together to produce a global score ranging from 0 to 21. Global scores above five indicate poor sleepers, such a finding being reported to have a high sensitivity (90%–99%) and specificity (84%–87%) (Carpenter & Andrykowski, 1998).

The ESS is a simple, self-administered questionnaire used to evaluate daytime sleepiness by means of eight items. The subject is asked to assess the probability of falling asleep in eight common situations that most people experience in daily life. The ESS scores for each item range from 1 to 3, 3 indicating the greatest probability. The total ESS score is the sum of these items, the maximum score therefore being 24 with a cutoff value of 10. Scores in the range of 0–9 are considered normal, and those in the range of 10–24 indicate a level of daytime sleepiness that warrants medical advice (Johns, 1991, 1992).

2.4 | Assessment of the level of depression and anxiety

The HAM-D is a rating scale used to evaluate the severity of depressive symptoms. It includes a consideration of 21 items with the score ranging from 0 to 54. A score greater than 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 (Hamilton, 1960).

The HAM-A is a rating scale developed to measure the severity of anxiety symptoms. It evaluates 14 items, each defined by a series of symptoms. Scores can range from 0 to 56. A score below 17 indicates mild anxiety, scores in the 18–24 range indicate mild to moderate anxiety, and scores from 25 to 30 indicate moderate to severe anxiety. The test provides an assessment of the degree of overall anxiety, psychic anxiety, and somatic anxiety. It is also used to assess the efficacy of anxiolytic and other psychotropic drugs in improving levels of anxiety (Hamilton, 1958).

2.5 | Assessment of pain

The numerical rating scale (NRS-11) is used for an assessment of the intensity of pain (pain and burning). The test is administered by means of an interview performed by a clinician who asks the patient to give a rating to reflect the degree of pain. The scale ranges from 0 to 10, with 0 indicating the absence of any oral symptoms and 10 indicating the worst imaginable symptom intensity. The NRS is a well-validated instrument, which is easy to administer. It is therefore frequently recommended for pain assessment, particularly for an evaluation of the degree of analgesia in response to treatment.

The T-PRI of the Short form of the McGill Pain Questionnaire (SF-MPQ) of Melzack is a validated multidimensional test of perceived pain. It gives useful information on the sensory and affective dimensions of the experience of pain. It is a self-report questionnaire consisting of 15 descriptors [11 sensory (descriptors 1–11) and four affective (descriptors 12–15)]. Each descriptor is ranked on an intensity scale ranging from 0 to 3, 0 indicating the absence of any discomfort and 3 indicating severe pain. The total T-PRI score is calculated by adding together the item scores (the total score therefore ranging from 0 to 45). There is no established critical cut point for score interpretation but obviously, as for the MPQ, the higher is the score the worse is the pain (Hawker, Mian, Kendzerska, & French, 2011).

2.6 | Statistical analysis

Demographic and clinical parameters and scales have been summarized using classic descriptive statistics. Differences between BMS patients and controls have been tested by the two-samples *t* test, for normal distributions, and by the Mann–Whitney procedure for non-normal data.

The significance of the relationship between any qualitative variables has been measured by the Pearson chi-square test. Differences associated with *p* values less than .05 or .01 have been considered moderately or strongly significant, respectively.

The odds of sleep disturbance, sociodemographic characteristics, and confounding factors among BMS patients and controls have been calculated using unconditional logistic regression. The internal consistency of the PSQI has been measured by the Cronbach's alpha test to estimate the reliability of the scores.

The importance of disease-related and psychological factors as determinants of sleep quality has been measured with multiple regression analyses considering, at the same time, the effect of demographic characteristics.

3 | RESULTS

The demographic and clinical findings relating to the patients and controls are summarized in Table 1.

TABLE 1 Sociodemographic and clinical characteristics of BMS patients and control subjects

Demographic variables	BMS patients, <i>n</i> = 200 Mean ± <i>SD</i>	Control patients, <i>n</i> = 200 Mean ± <i>SD</i>	<i>p</i> -Value
Age	61.92 ± 12.16	53.91 ± 9.81	<.001**
Years of education	9.23 ± 4.00	10.20 ± 4.24	.019*
Gender			
Male	37 (18.5%)	64 (32.0%)	.002**
Female	163 (81.5%)	136 (68.0%)	
Family status			
Married	153 (76.5%)	147 (73.5%)	.565
Single	17 (8.5%)	21 (10.5%)	
Divorced	11 (5.5%)	23 (11.5%)	
Widowed	19 (9.5%)	9 (4.5%)	
Employment status			
Employed	57 (28.5%)	123 (61.5%)	<.001**
Retired	89 (44.5%)	28 (14.0%)	
Unemployed	54 (27.0%)	49 (24.5%)	
Clinical parameters	Median–IQR	Median–IQR	<i>p</i> -Value
PSQI	9 [6–12]	4 [2–5]	<.001**
HAM-D	13 [8–20]	4 [2–6]	<.001**
HAM-A	16 [9–22]	5 [2–6]	<.001**
ESS	5 [2–9]	3 [2–4]	<.001**
NRS	7 [4–8]	0 [0–0]	<.001**
T-PRI	9 [5–14]	0 [0–0]	<.001**

IQR, interquartile range; BMS, burning mouth syndrome; PSQI, Pittsburgh Sleep Quality Index; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; ESS, Epworth Sleepiness Scale; NRS, Numeric Pain Intensity Scale; T-PRI, Total Pain Rating Index. The significance of the relationship between the qualitative variables was measured by the Pearson chi-square test. The significance of the difference between the means was measured by the two-samples *t* test. The significance of the difference between the medians was measured by the Mann–Whitney *U* test.

*Moderately significant .01 < *p* ≤ .05.

**Strongly significant *p* ≤ .01.

TABLE 2 Odds of PSQI and confounding factors among BMS patients and controls

Variables	OR	p Value	95% CI for OR
PSQI	1.196	.002**	1.069–1.338
Age	1.042	.017**	1.007–1.077
Education	1.044	.323	0.958–1.137
Female	1.401	.358	0.683–2.872
Married	0.939	.858	0.474–1.861
Employed	0.549	.110	0.263–1.145
HAM-D	1.194	<.001**	1.086–1.313
HAM-A	1.116	.006**	1.032–1.207
ESS	0.982	.721	0.888–1.085

BMS, burning mouth syndrome; PSQI, Pittsburgh Sleep Quality Index; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; ESS, Epworth Sleepiness Scale; OR, odds ratio. ORs have been calculated using unconditional logistic regression.

*Moderately significant .01 < $p \leq .05$.

**Strongly significant $p \leq .01$.

The BMS patients and controls showed significant differences in age, education, gender, and employment status. The mean age of the BMS patients and controls was 61.92 ± 12.16 and 53.91 ± 9.81 years, respectively. The mean of years of education was 9.23 ± 4.00 for the patients and 10.20 ± 4.24 for the controls. The controls are characterized by a significantly higher percentage of employment and a higher proportion of males than the BMS patients.

In our study, the patients and controls are not matched due to the large sample size. Case-control matching is very difficult to obtain, especially when the matching is related to several factors (Song & Chung, 2010).

Therefore, we evaluated the effect of confounding factors through an unconditional logistic regression. The results are shown in Table 2.

Table 2 shows that the odds ratios of the sociodemographic factors between the BMS patients and controls, except for age, do not have significant values.

The ratio of the odds of the PSQI among the cases and controls, adjusted for confounding and demographic factors, was significantly higher than 1 (OR1.196).

3.1 | PSQI reliability

In Table 3, we report the reliability analysis of the PSQI components in the BMS patients. A Cronbach's α greater than .7 and an item-scale correlation greater than 0.3 indicate a satisfactory overall reliability and a good item contribution to the scale, respectively.

3.2 | Sleep quality

The global and component scores for the PSQI were significantly different between the patients and controls (Tables 1 and 4).

Patients with BMS had higher mean PSQI scores, indicating a poorer sleep quality for these patients compared to the healthy

TABLE 3 Reliability analysis of the Pittsburgh Sleep Quality Index (PSQI) scale in burning mouth syndrome (BMS) patients and control subjects

PSQI components	BMS cases	Control cases
	Item-scale correlation ρ	
Subjective sleep quality	0.55	0.41
Sleep latency	0.56	0.37
Sleep duration	0.66	0.48
Habitual sleep efficiency	0.65	0.33
Sleep disturbances	0.36	0.24*
Use of sleep medications	0.22*	0.47
Daytime dysfunction	0.34	0.13*
Cronbach's alpha	0.76	0.65

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

controls; 158 patients (79%) were poor sleepers with a PSQI global score greater than 5. Among the BMS patients, the clinical parameters of good (PSQI < 5) and poor (PSQI > 5) sleepers were compared. Depression (HAM-D), anxiety (HAM-A) and daytime sleepiness (ESS) were found to be significantly different between the two groups ($p < .001$), while intensity and quality of pain were not ($p = .069$) (Table 5). However, the value of the ESS was lower than the cutoff of 10 in the poor (median 3) and good sleepers (median 6).

3.3 | Dependence of sleep quality

Table 6 shows the positive correlation between depression (HAM-D) anxiety (HAM-A) and quality of pain (T-PRI) with sleep quality, and the poor correlation between pain intensity (NRS) and daytime sleepiness (ESS) with sleep quality.

In addition, in the analysis of the demographic characteristics, years of education correlated negatively with sleep quality and marital status and job status were poorly correlated with sleep quality.

3.4 | Association with sleep quality

The results of the simultaneous multiple linear regression analyses predicting sleep quality are shown in Table 7.

The model testing the contribution of the demographic variables and confounding factors to sleep quality was found to be statistically significant ($R^2 = 44.5\%$ $p \leq .001$).

Considering demographic variables, only age and marital status were significant. In addition, anxiety and depression were confirmed to have a strong effect on sleep quality.

4 | DISCUSSION

Burning mouth syndrome is a complex disorder, frequently associated with extra-oral somatic comorbidity and psychiatric illnesses such

PSQI components	BMS cases			Control cases			p-Value
	Median	IQR	Range	Median	IQR	Range	
Subjective sleep quality	1	1-2	0-3	1	0-1	0-2	<.001**
Sleep latency	1	0-2	0-3	0	0-1	0-3	<.001**
Sleep duration	1	0-2	0-3	1	0-1	0-3	<.001**
Habitual sleep efficiency	1	0-2	0-5	0	0-1	0-3	<.001**
Sleep disturbances	1	1-2	0-3	1	1-1	0-3	<.001**
Use of sleep medications	1	0-3	0-3	0	0-0	0-3	<.001**
Daytime dysfunction	1	0-3	0-3	0	0-0	0-2	<.001**

TABLE 4 Comparison of components of the PSQI in BMS patients and control subjects

IQR, interquartile range. BMS, burning mouth syndrome; PSQI, Pittsburgh Sleep Quality Index. The significance of the difference between the medians was measured by the Mann-Whitney *U* test. *Moderately significant .01 < *p* ≤ .05. **Strongly significant *p* ≤ .01.

TABLE 5 Comparison between BMS patient good and poor sleepers

PSQI components	PSQI ≤ 5 (n = 42, 21.0%)			PSQI > 5 (n = 158, 79.0%)			p-Value
	Median	IQR	Range	Median	IQR	Range	
Depression (HAM-D)	6	2-11	0-22	16	10-21	6-36	<.001**
Anxiety (HAM-A)	8	3-16	0-25	18	13-22	12-56	<.001**
Daytime sleepiness (ESS)	3	0-6	0-12	6	3-9	0-17	<.001**
NRS	5	4-8	0-10	7	4-8	0-10	.069
T-PRI	7	4-11	0-36	9	6-15	0-40	.069
	Frequencies (%)			Frequencies (%)			p-Value
Depression (HAM-D)							
0-9	29 (69.0%)			39 (24.7%)			<0.001**
10-17	11 (26.2%)			53 (33.5%)			
18-24	2 (4.8%)			45 (28.5%)			
>24	0 (0%)			21 (13.3%)			
Anxiety (HAM-A)							
0-17	34 (81.0%)			76 (48.1%)			<0.001**
18-24	7 (16.7%)			47 (29.7%)			
>24	1 (2.4%)			35 (21.5%)			

IQR, interquartile range; BMS, burning mouth syndrome; PSQI, Pittsburgh Sleep Quality Index; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; ESS, Epworth Sleepiness Scale; NRS, Numeric Pain Intensity Scale; T-PRI, Total Pain Rating Index. The significance difference between the medians was measured by the Mann-Whitney *U* test. *Moderately significant .01 < *p*-value ≤ .05. **Strongly significant *p*-value ≤ .01.

as depression, anxiety, and SD (Galli, Lodi, Sardella, & Vegni, 2016; Maina et al., 2005; Mignogna et al., 2011).

Previous research articles have analyzed the role of sleep dysfunction in BMS; in our previous study, we found a prevalence of SD, including insomnia and daytime sleepiness, in 80% of patients with BMS (Schivone et al., 2012). In accordance with our data, Lopez-Jornet et al. (2015) found SD in 67.1% of patients with BMS compared with

a control group of healthy subjects. Adamo et al. (2013) and Arbabi-Kalati, Bakhshani, Tahmtan, and Movahedinejad (2015) found SD in 78% of patients with BMS vs 38.7% of healthy subjects.

In addition, a recent retrospective work on 47,941 Taiwanese patients with SD has demonstrated that poor sleep increases the risk of BMS, highlighting the importance of sleep impairment in this disease (Lee et al., 2014).

TABLE 6 Dependence of sleep quality with clinical parameters and demographic characteristics for BMS patients

Clinical parameters		Pearson ρ coefficient	p -Value
Depression (HAM-D)		0.570	<.001**
Anxiety (HAM-A)		0.549	<.001**
Daytime sleepiness (ESS)		0.159	.024*
NRS		0.162	.021*
T-PRI		0.191	.006**
Demographic characteristics		Pearson ρ coefficient	p -Value
Age		0.197	.005**
Years of education		-0.099	.159
	Median—IQR	Median—IQR	p -Value
Gender	Male	Female	.613
	9.0; [5.5–12.3]	9.0; [6.0–12.0]	
Marital status	Yes	No	.030*
	9.0; [6.0–13.0]	8.0; [4.3–9.8]	
Employment	Yes	No	.015*
	8.0; [4.0–11.0]	9.0; [7.0–13.0]	

IQR, interquartile range; BMS, burning mouth syndrome; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; ESS, Epworth Sleepiness Scale; NRS, Numeric Pain Intensity Scale; T-PRI, Total Pain Rating Index.

For the numerical variables, the p -values were obtained by the Pearson correlation test. For the qualitative characteristics, the p -values were obtained by the Mann-Whitney test.

*Moderately significant .01 < p -value \leq .05.

**Strongly significant p -value \leq .01.

In this present Italian multicenter study, in agreement with the findings of other studies reported in literature, we have found a prevalence of SD in 79% (158) of BMS patients.

In contrast with our previous study, we did not find any daytime sleepiness in the poor sleeper patients with BMS. However, in the literature, patients with insomnia reported, over time, daytime functional impairment, with sleepiness, and concentration and memory loss (Ancoli-Israel & Roth, 1999). Therefore, these data are possibly related to a more recent onset of SD in our sample of patients.

Regarding the association of mood disorders with chronic pain and with BMS, it is well known, as several studies have demonstrated, that anxiety and depression may be important causative and aggravating factors in BMS (Buljan, Savić, & Karlović, 2008). In a recent review article, Galli et al. (2016) confirmed that psychiatric factors play a role in BMS and that anxiety and depression seem to be the most common comorbid diseases among patients with BMS.

In our sample, we found mild depression and mild anxiety in the patients with BMS compared with the healthy subjects. In the poor sleeper BMS patients, we found a higher prevalence of moderate and severe depression (41.8%), and a higher prevalence of moderate and severe anxiety (51.2%) suggesting also an important relationship between sleep and mood. These data are confirmed in the dependence analysis in Table 7 (p value < .001**) and remain significant in the multiple simultaneous regression analyses confirming

TABLE 7 Multiple linear regression model predicting sleep quality in BMS patients

Predictors	Beta	SE	T statistics	p -Value
Intercept	-2.091	2.223	-0.941	.348
Age	0.080	0.025	3.223	.001**
Years of education	0.029	0.074	0.399	.691
Gender: female	0.268	0.630	0.426	.671
Marital status: married	1.495	0.566	2.643	.009**
Occupation: yes	-0.004	0.679	-0.006	.995
Depression (HAM-D)	0.207	0.045	4.587	<.001**
Anxiety (HAM-A)	0.131	0.039	3.391	.001**
Daytime sleepiness (ESS)	0.082	0.067	1.234	.219
NRS	-0.115	0.115	-1.002	.318
T-PRI	-0.022	0.041	-0.552	.582
Model goodness of fit statistics				
$R^2 = 41.4\%$; F statistics = 14.76; p -value < .001**				

BMS, burning mouth syndrome; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; ESS, Epworth Sleepiness Scale; NRS, Numeric Pain Intensity Scale; T-PRI, Total Pain Rating Index.

SE are the standard errors of the beta estimates. The p -values were obtained by the hypothesis test on regression coefficients.

*Moderately significant .01 < p -value \leq .05.

**Strongly significant p -value \leq .01.

that depression and anxiety may be important risk factors of SD in BMS patients. However, while in our previous study the standard multiple regression analysis of the final full model in which all the variables were entered simultaneously could explain 62% of the variance in sleep quality, in the current study the model could explain only 44.5% of the variance. These data highlight that anxiety and depression have an important role in sleep quality, but that, sometimes, poor sleep in BMS patients may be an independent factor that should be analyzed and treated separately. Furthermore, as it is an independent factor, it could have an onset before that of the BMS symptoms.

Although it is widely assumed that SD is a common comorbidity with psychiatric disorders, most notably in major depression, and should be considered as an associate symptom (secondary insomnia), more recently accumulative evidence has suggested that insomnia is not necessarily an epiphenomenon, and should be considered as a separate disease/disorder (primary insomnia).

The authors of such studies have hypothesized that insomnia has been considered as a primary disorder only in the absence of any clinically relevant psychiatric disease (Baglioni et al., 2011; Harvey, 2001).

Primary insomnia is also a predictor of depression; individuals with SD, especially women, have a higher risk of developing depression (Baglioni et al., 2011; Riemann & Voderholzer, 2003). Time sequence analysis from several studies shows that the onset

of insomnia can precede, even by several years, the first onset of depression in many cases (Johnson, Roth, & Breslau, 2006; Ohayon & Roth, 2003). Riemann and Voderholzer (2003) reported that symptoms of insomnia for a period of at least 2 weeks predict an increased risk of developing depression within the following 3 years. It would seem that insomnia has a higher predictive value for future depression than anxiety (Jansson-Fröjmark & Lindblom, 2008; Morphy, Dunn, Lewis, Boardman, & Croft, 2007).

In addition, SD also plays an important role in depression relapse and the transitioning of depression into a chronic state because it can represent a residual phase of a major mood disorder (Falussy, Balla, & Frecska, 2014; Perlis et al., 2006).

In this context, the early detection and treatment of SD in BMS patients without any history of depression and any evidence of anxiety and depression (HAM-D and HAM-A < 7) can result in both a significant improvement in the patient's quality of life and also in the prevention of secondary mood disorders. In addition, in patients with BMS, with anxiety and depression with an SD comorbidity, the treatment of residual insomnia is necessary not only to aid the remission of depression but also to prevent any relapse.

Moreover, changes in sleep patterns are a part of the normal aging process and increasing age is associated with insomnia (Schubert et al., 2002); these data were confirmed in our study by the multiple simultaneous regression analyses in which age is an important risk factor of SD.

In addition, we found a correlation between marital status and SD in which married patients are prone to develop insomnia; this is possible considering that a negative marital relationship increased the risk of insomnia symptoms through an increase in mood disorders; these data were confirmed by a previous study (Chen, Waite, & Lauderdale, 2015).

Regarding the relationships between pain and SD in our sample patients with BMS, no statistically significant differences in the quality and intensity of pain between the poor and good sleepers with BMS were found, because the NRS and T-PRI values were higher in both groups (the median values of the NRS and T-PRI in the good sleepers were 5 and 7 and in the bad sleepers 7 and 9, respectively). This result was in accordance with our previous study (Schiavone et al., 2012) but in contrast with the study of Lopez-Jornet et al. (2015) where poor sleeper BMS patients were prone to increased pain.

The relationship between SD and pain is complex and not completely understood; significant research studies report that this relationship is bidirectional (Fishbain, Hall, Meyers, Gonzales, & Mallinckrodt, 2008).

Sleep disturbance is frequently reported by patients afflicted by chronic pain, but it is often seen as a secondary symptom rather than an independent symptom. Because pain mediates sleep problems, adequate pain management is thought to lead to improved sleep in patients with chronic pain (Park, Yoon, Yoon, Moon, & Kim, 2016; Power, Perruccio, & Badley, 2005).

However, this point of view has shifted over time with new evidence suggesting insomnia as the primary disorder from which chronic pain often develops (Asih, Neblett, Mayer, Brede, & Gatchel,

2014); recently, Finan, Goodin, and Smith (2013) have found that sleep impairments are a reliable predictor of the recurrence and worsening of chronic pain, to a greater extent than pain predicts sleep impairments. In agreement, Walsh, Muehlbach, Lauter, Hilliker, and Schweitzer (1996) showed that benzodiazepine, by enhancing sleep quality, relieved the subjective symptoms of joint pain in patients with rheumatoid arthritis even when there was no objective improvement.

These data have been confirmed by research suggesting that many patients with chronic pain continue to experience sleep problems even when good pain control is achieved while an improvement of insomnia results in better pain treatment outcomes in these patients (Gustavsson & von Koch, 2006; Tang, 2008).

From a biophysiological perspective, insomnia is linked to a higher production of inflammatory mediators, which can potentially aggravate pain, causing a hyperalgesic state with a low pain threshold, and leading to an inability to sufficiently activate the pain inhibitory pathways (Haack et al., 2012). This effect remains even after the other psychological symptoms are controlled (Quartana, Finan, Page, & Smith, 2015; Spiegel, Leproult, & Van Cauter, 1999).

Moreover, in patients suffering from a major depressive disorder, insomnia is a significant predictor of pain, even after checking for the severity of anxiety and depression (Ohayon, 2007).

In our study, a clear relationship between insomnia and pain could not be established because the intensity of pain was higher in both good and poor sleepers. A possible bias of our study could be the lack of any analysis of the duration either of the illness or the insomnia; it may not be unlikely that prolonged pain, over time, may cause SD as well as that persistent insomnia may worsen the perception of symptoms in patients with BMS, contributing to an exacerbation of the disease.

This study has highlighted the complexity of BMS in which it is necessary to consider the psychological profile of BMS patients, and the presence of pain and insomnia, to have a more complete assessment. Anxiety, depression, and sleep are, in some cases, interconnected, each affecting each other. SD and mood disorders lead to a continuously perpetuating cycle and can aggravate BMS and prevent healing. However, many patients may have a primary insomnia that requires a specific assessment and treatment.

Finally, the findings from this study lead to the conclusion that sleep quality should also be considered in the treatment approach for BMS because the management of SD may not only ameliorate the symptoms of BMS but also aid depression remission and/or prevent late-life depression.

4.1 | Study limitations

Our study has several limitations that suggest directions for future research.

First, our findings are cross-sectional in nature, limiting our ability to identify a causal relationship between psychological factors, pain, and sleep disturbance. Prospective and longitudinal studies with a clear temporal precedence and causality are needed to evaluate the

influence of psychological symptoms and insomnia on pain intensity in BMS.

Secondly, the sleep assessment was based on self-report questionnaires without any confirmation by full-night polysomnographic studies of poor sleeper patients. However, questionnaires could be considered as an initial evaluation of SD and subsequently integrated with other diagnostic investigations in patients with impaired sleep.

5 | CONCLUSIONS

This is the largest multicentre study that has confirmed the comorbidity of sleep disturbances and mood disorders in patients with BMS suggesting that SD and mood disorders are a common problem and an aggravating factor in BMS. In contrast, pain intensity and quality did not correlate with sleep quality.

These findings confirm the necessity of a multidisciplinary team approach in which a close collaboration between dentists, psychiatrists, psychologists, and neurologists is required for the evaluation of comorbidities and for a suitably individualized sequential treatment of patients.

Clinicians could evaluate therapies not only to reduce pain but to improve sleep and to reduce levels of anxiety and depression, considering antidepressant and anticonvulsants in the management of patients with BMS. Treatment should be individualized for each patient in relation to the patient's age, gender, comorbidity, systemic diseases, and drug intake.

Future studies should try to better understand the relationships between pain, SD, and mood disorders to determine which of these conditions occurs first and, accordingly, which strategy is the most effective in terms of improving the treatment of BMS.

CONFLICT OF INTEREST

All of the authors declare that they do not have any conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed in the research design, acquisition, analysis and interpretation of data. All authors have approved the final version of the paper.

ETHICAL APPROVAL

This study has been carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the individual participants included in the study.

ORCID

D Adamo  <http://orcid.org/0000-0002-3784-4229>

M Pentenero  <http://orcid.org/0000-0003-3972-1203>

REFERENCES

- Abetz, L. M., & Savage, N. W. (2009). Burning mouth syndrome and psychological disorders. *Australian Dental Journal*, 54(2), 84–93. <https://doi.org/10.1111/j.1834-7819.2009.01099.x>
- Adamo, D., Celentano, A., Ruoppo, E., Cucciniello, C., Pecoraro, G., Aria, M., & Mignogna, M. D. (2015). The relationship between sociodemographic characteristics and clinical features in burning mouth syndrome. *Pain Medicine (Malden, Mass.)*, 16(11), 2171–2179. <https://doi.org/10.1111/pme.12808>
- Adamo, D., Schiavone, V., Aria, M., Leuci, S., Ruoppo, E., Dell'Aversana, G., & Mignogna, M. D. (2013). Sleep disturbance in patients with burning mouth syndrome: A case-control study. *Journal of Orofacial Pain*, 27(4), 304–313. <https://doi.org/10.11607/jop.1109>
- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*, 5th ed. Washington, DC: APA.
- Ancoli-Israel, S., & Roth, T. (1999). Characteristics of insomnia in the United States: Results of the 1991 National Sleep Foundation Survey. I. *Sleep*, 1(22 Suppl 2), S347–S353.
- Arbabi-Kalati, F., Bakhshani, N. M., Tahmtan, B., & Movahedinejad, F. (2015). Association of impaired sleep quality in patients with burning mouth syndrome: A case-control study. *Health Scope*, 4(2), e23795.
- Asih, S., Neblett, R., Mayer, T. G., Brede, E., & Gatchel, R. J. (2014). Insomnia in a chronic musculoskeletal pain with disability; population is independent of pain and depression. *Spine Journal*, 14, 2000–2007.
- Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., ... Riemann, D. (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders*, 135(1–3), 10–19. <https://doi.org/10.1016/j.jad.2011.01.011>
- Benca, R. M., & Peterson, M. J. (2008). Insomnia and depression. *Sleep Medicine*, 9(Suppl 1), S3–S9. [https://doi.org/10.1016/S1389-9457\(08\)70010-8](https://doi.org/10.1016/S1389-9457(08)70010-8)
- Billiard, M., & Bentley, A. (2004). Is insomnia best categorized as a symptom or a disease? *Sleep Medicine*, 5(Suppl 1), S35–S40. [https://doi.org/10.1016/S1389-9457\(04\)90006-8](https://doi.org/10.1016/S1389-9457(04)90006-8)
- Buljan, D., Savić, I., & Karlović, D. (2008). Correlation between anxiety, depression and burning mouth syndrome. *Acta Clinica Croatica*, 47(4), 211–216.
- Carpenter, J. S., & Andrykowski, M. A. (1998). Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of Psychosomatic Research*, 45, 5–13. [https://doi.org/10.1016/S0022-3999\(97\)00298-5](https://doi.org/10.1016/S0022-3999(97)00298-5)
- Chainani-Wu, N., Madden, E., & Silverman, Jr, S. (2011). A case-control study of burning mouth syndrome and sleep dysfunction. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, 112(2), 203–208. <https://doi.org/10.1016/j.tripleo.2011.03.014>
- Charleston, L. (2013). Burning mouth syndrome: A review of recent literature. *Current Pain and Headache Reports*, 17(6), 336. <https://doi.org/10.1007/s11916-013-0336-9>
- Chen, J. H., Waite, L. J., & Lauderdale, D. S. (2015). Marriage, relationship quality, and sleep among U.S. older adults. *Journal of Health and Social Behavior*, 56(3), 356–377. <https://doi.org/10.1177/0022146515594631>
- Chung, K. F., & Tso, K. C. (2010). Relationship between insomnia and pain in major depressive disorder: A sleep diary and actigraphy study. *Sleep Medicine*, 11(8), 752–758. <https://doi.org/10.1016/j.sleep.2009.09.005>
- Cox, R. C., & Olatunji, B. O. (2016). A systematic review of sleep disturbance in anxiety and related disorders. *Journal of Anxiety Disorders*, 37, 104–129. <https://doi.org/10.1016/j.janxdis.2015.12.001>
- de Tommaso, M., Delussi, M., Vecchio, E., Scirucchio, V., Invitto, S., & Livrea, P. (2014). Sleep features and central sensitization symptoms in primary headache patients. *The Journal of Headache and Pain*, 15, 64. <https://doi.org/10.1186/1129-2377-15-64>

- Falussy, L., Balla, P., & Frecska, E. (2014). Relaxation and insomnia in unipolar major depression. *Neuropsychopharmacologia Hungarica*, 16(3), 141–147.
- Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: An update and a path forward. *The Journal of Pain*, 14(12), 1539–1552. <https://doi.org/10.1016/j.jpain.2013.08.007>
- Finan, P. H., & Smith, M. T. (2013). The comorbidity of insomnia, chronic pain, and depression: Dopamine as putative mechanism. *Sleep Medicine Reviews*, 17, 173–183. <https://doi.org/10.1016/j.smr.2012.03.003>
- Fishbain, D. A., Hall, J., Meyers, A. L., Gonzales, J., & Mallinckrodt, C. (2008). Does pain mediate the pain interference with sleep problem in chronic pain? Findings from studies for management of diabetic peripheral neuropathic pain with duloxetine. *Journal of Pain and Symptom Management*, 36, 639–647. <https://doi.org/10.1016/j.jpainsym.2007.12.012>
- Frutos, R., Rodríguez, S., Miralles-Jorda, L., & Machuca, G. (2002). Oral manifestations and dental treatment in menopause. *Medicina Oral*, 7(1), 26–30, 31–5.
- Galli, F., Lodi, G., Sardella, A., & Vegni, E. (2016). Role of psychological factors in burning mouth syndrome: A systematic review and meta-analysis. *Cephalalgia*, 37(3), 265–277.
- Grushka, M., Epstein, J. B., & Gorsky, M. (2002). Burning mouth syndrome. *American Family Physician*, 65(4), 615–620.
- Grushka, M., Epstein, J. B., & Gorsky, M. (2003). Burning mouth syndrome and other oral sensory disorders: A unifying hypothesis. *Pain Research & Management*, 8(3), 133–135. <https://doi.org/10.1155/2003/654735>
- Gustavsson, C., & von Koch, L. (2006). Applied relaxation in the treatment of long-lasting neck pain: A randomized controlled pilot study. *Journal of Rehabilitation Medicine*, 38, 100–107. <https://doi.org/10.1080/16501970510044025>
- Haack, M., Scott-Sutherland, J., Santangelo, G., Simpson, N. S., Sethna, N., & Mullington, J. M. (2012). Pain sensitivity and modulation in primary insomnia. *European Journal of Pain*, 16, 522–533. <https://doi.org/10.1016/j.ejpain.2011.07.007>
- Hagelberg, N., Jääskeläinen, S. K., Martikainen, I. K., Mansikka, H., Forssell, H., Scheinin, H., ... Pertovaara, A. (2004). Striatal dopamine D2 receptors in modulation of pain in humans: A review. *European Journal of Pharmacology*, 500, 187–192. <https://doi.org/10.1016/j.ejphar.2004.07.024>
- Hamilton, M. (1958). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, 32, 50–55.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56–62. <https://doi.org/10.1136/jnnp.23.1.56>
- Harvey, A. G. (2001). Insomnia: Symptom or diagnosis? *Clinical Psychology Review*, 22(7), 1037–1059. [https://doi.org/10.1016/S0272-7358\(00\)00083-0](https://doi.org/10.1016/S0272-7358(00)00083-0)
- Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care & Research*, 63(Suppl 11), S240–S252. <https://doi.org/10.1002/acr.20543>
- Headache Classification Committee of the International Headache Society (2013). The International classification of headache disorders, 3rd edition (beta version). *Cephalalgia*, 33, 629–808.
- Jääskeläinen, S. K., & Woda, A. (2017). Burning mouth syndrome. *Cephalalgia*, 37(7), 627–647. <https://doi.org/10.1177/0333102417694883>
- Jansson-Fröjmark, M., & Lindblom, K. (2008). A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. *Journal of Psychosomatic Research*, 64(4), 443–449. <https://doi.org/10.1016/j.jpsychores.2007.10.016>
- Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, 14, 540–545. <https://doi.org/10.1093/sleep/14.6.540>
- Johns, M. W. (1992). Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, 15, 376–381. <https://doi.org/10.1093/sleep/15.4.376>
- Johnson, E. O., Roth, T., & Breslau, N. (2006). The association of insomnia with anxiety disorders and depression: Exploration of the direction of risk. *Journal of Psychiatric Research*, 40(8), 700–708. <https://doi.org/10.1016/j.jpsychores.2006.07.008>
- Lee, E., Cho, H. J., Olmstead, R., Levin, M. J., Oxman, M. N., & Irwin, M. R. (2013). Persistent sleep disturbance: A risk factor for recurrent depression in community-dwelling older adults. *Sleep*, 36(11), 1685–1691.
- Lee, C. F., Lin, K. Y., Lin, M. C., Lin, C. L., Chang, S. N., & Kao, C. H. (2014). Sleep disorders increase the risk of burning mouth syndrome: A retrospective population-based cohort study. *Sleep Medicine*, 15(11), 1405–1410. <https://doi.org/10.1016/j.sleep.2014.06.009>
- Lopez-Jornet, P., Lucero-Berdugo, M., Castillo-Felipe, C., Zamora Lavella, C., Ferrandez-Pujante, A., & Pons-Fuster, A. (2015). Assessment of self-reported sleep disturbance and psychological status in patients with burning mouth syndrome. *Journal of the European Academy of Dermatology and Venereology*, 29(7), 1285–1290. <https://doi.org/10.1111/jdv.12795>
- Maina, G., Albert, U., Gandolfo, S., Vitalucci, A., & Bogetto, F. (2005). Personality disorders in patients with burning mouth syndrome. *Journal of Personality Disorders*, 19(1), 84–93. <https://doi.org/10.1521/pedi.19.1.84.62182>
- Mignogna, M. D., Pollio, A., Fortuna, G., Leuci, S., Ruoppo, E., Adamo, D., & Zarrelli, C. (2011). Unexplained somatic comorbidities in patients with burning mouth syndrome: A controlled clinical study. *Journal of Orofacial Pain*, 25(2), 131–140.
- Morin, C. M., LeBlanc, M., Bélanger, L., Ivers, H., Mérette, C., & Savard, J. (2011). Prevalence of insomnia and its treatment in Canada. *Canadian Journal of Psychiatry*, 56(9), 540–548. <https://doi.org/10.1177/070674371105600905>
- Morphy, H., Dunn, K. M., Lewis, M., Boardman, H. F., & Croft, P. R. (2007). Epidemiology of insomnia: A longitudinal study in a UK population. *Sleep*, 30(3), 274–280.
- Neckelmann, D., Mykletun, A., & Dahl, A. A. (2007). Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep*, 30(7), 873–880. <https://doi.org/10.1093/sleep/30.7.873>
- Ohayon, M. M. (2007). Insomnia: A ticking clock for depression? *Journal of Psychiatric Research*, 41(11), 893–894. <https://doi.org/10.1016/j.jpsychores.2007.07.008>
- Ohayon, M. M. (2009). Pain sensitivity, depression, and sleep deprivation: Links with serotonergic dysfunction. *Journal of Psychiatric Research*, 43(16), 1243–1245. <https://doi.org/10.1016/j.jpsychores.2009.10.007>
- Ohayon, M. M., & Roth, T. (2003). Place of chronic insomnia in the course of depressive and anxiety disorders. *Journal of Psychiatric Research*, 37(1), 9–15. [https://doi.org/10.1016/S0022-3956\(02\)00052-3](https://doi.org/10.1016/S0022-3956(02)00052-3)
- Park, S. J., Yoon, D. M., Yoon, K. B., Moon, J. A., & Kim, S. H. (2016). Factors associated with higher reported pain levels in patients with chronic musculoskeletal pain: A cross-sectional. Correlational analysis. *PLoS ONE*, 11(9), e0163132. <https://doi.org/10.1371/journal.pone.0163132>
- Patel, S. R., & Hu, F. B. (2008). Short sleep duration and weight gain: A systematic review. *Obesity*, 16(3), 643–653. <https://doi.org/10.1038/oby.2007.118>
- Perlis, M. L., Smith, L. J., Lyness, J. M., Matteson, S. R., Pigeon, W. R., Jungquist, C. R., & Tu, X. (2006). Insomnia as a risk factor for onset of depression in the elderly. *Behavioral Sleep Medicine*, 4(2), 104–113. https://doi.org/10.1207/s15402010bsm0402_3
- Power, J. D., Perruccio, A. V., & Badley, E. M. (2005). Pain as a mediator of sleep problems in arthritis and other chronic conditions.

- Arthritis and Rheumatism, 53, 911–919. [https://doi.org/10.1002/\(ISSN\)1529-0131](https://doi.org/10.1002/(ISSN)1529-0131)
- Quartana, P. J., Finan, P. H., Page, G. G., & Smith, M. T. (2015). Effects of insomnia disorder and knee osteoarthritis on resting and pain-evoked inflammatory markers. *Brain, Behavior, and Immunity*, 47, 228–237. <https://doi.org/10.1016/j.bbi.2014.12.010>
- Riemann, D., & Voderholzer, U. (2003). Primary insomnia: A risk factor to develop depression? *Journal of Affective Disorders*, 76(1–3), 255–259. [https://doi.org/10.1016/S0165-0327\(02\)00072-1](https://doi.org/10.1016/S0165-0327(02)00072-1)
- Roy, A. N., & Smith, M. (2010). Prevalence and cost of insomnia in a state Medicaid fee-for-service population based on diagnostic codes and prescription utilization. *Sleep Medicine*, 11(5), 462–469. <https://doi.org/10.1016/j.sleep.2009.09.012>
- Rumble, M. E., White, K. H., & Benca, R. M. (2015). Sleep disturbances in mood disorders. *Psychiatric Clinics of North America*, 38(4), 743–759. <https://doi.org/10.1016/j.psc.2015.07.006>
- Scala, A., Checchi, L., Montevecchi, M., Marini, I., & Giamberardino, M. A. (2003). Update on burning mouth syndrome: Overview and patient management. *Critical Reviews in Oral Biology and Medicine*, 14(4), 275–291. <https://doi.org/10.1177/154411130301400405>
- Schiavone, V., Adamo, D., Ventrella, G., Morlino, M., De Notaris, E. B., Ravel, M. G., ... Mignogna, M. D. (2012). Anxiety, depression, and pain in burning mouth syndrome: First chicken or egg? *Headache*, 52(6), 1019–1025. <https://doi.org/10.1111/j.1526-4610.2012.02171.x>
- Schubert, C. R., Cruickshanks, K. J., Dalton, D. S., Klein, B. E., Klein, R., & Nondahl, D. M. (2002). Prevalence of sleep problems and quality of life in an older population. *Sleep*, 25, 889–893.
- Smagula, S. F., Stone, K. L., Fabio, A., & Cauley, J. A. (2016). Risk factors for sleep disturbances in older adults: Evidence from prospective studies. *Sleep Medicine Reviews*, 25, 21–30. <https://doi.org/10.1016/j.smr.2015.01.003>
- Smith, M. T., & Haythornthwaite, J. A. (2004). How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Medicine Reviews*, 8(2), 119–132. [https://doi.org/10.1016/S1087-0792\(03\)00044-3](https://doi.org/10.1016/S1087-0792(03)00044-3)
- Song, J. W., & Chung, K. C. (2010). Observational studies: Cohort and case-control studies. *Plastic and Reconstructive Surgery*, 126(6), 2234–2235. <https://doi.org/10.1097/PRS.0b013e3181f44abc>
- Spanemberg, J. C., Rodríguez de Rivera Campillo, C., Salas, E. J., & López López, J. (2014). Burning mouth syndrome: Update. *Oral Health and Dental Management*, 13(2), 418–424.
- Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep deprivation on metabolic and endocrine function. *Lancet*, 354, 1435–1439. [https://doi.org/10.1016/S0140-6736\(99\)01376-8](https://doi.org/10.1016/S0140-6736(99)01376-8)
- Sun, A., Wu, K. M., Wang, Y. P., Lin, H. P., Chen, H. M., & Chiang, C. P. (2013). Burning mouth syndrome: A review and update. *Journal of Oral Pathology and Medicine*, 42(9), 649–655. <https://doi.org/10.1111/jop.12101>
- Tang, N. K. (2008). Insomnia co-occurring with chronic pain: Clinical features, interaction, assessments and possible interventions. *Reviews in Pain*, 2, 2–7.
- Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of chronic insomnia with medical problems. *Sleep*, 30(7), 213–218. <https://doi.org/10.1093/sleep/30.2.213>
- Walsh, J. K., Muehlbach, M. J., Lauter, S. A., Hilliker, N. A., & Schweitzer, P. K. (1996). Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. *Journal of Rheumatology*, 23(2), 245–252.
- Walsh, J. K., Salkeld, L., Knowles, L. J., Tasker, T., & Hunneyball, I. M. (2010). Treatment of elderly primary insomnia patients with EVT 201 improves sleep initiation, sleep maintenance, and daytime sleepiness. *Sleep Medicine*, 11, 23–30. <https://doi.org/10.1016/j.sleep.2009.07.012>