A case-control study of burning mouth syndrome and sleep dysfunction

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Objective. The objective of this study was to evaluate whether sleep dysfunction is a risk factor for burning mouth syndrome (BMS).

Study design. An age- and sex-matched case-control study of patients with BMS and controls with various oral conditions was conducted. A numerical rating scale for oral discomfort and the sleep scale from the medical outcomes study were used for measurements, and statistical analyses included use of logistic regression models.

Results. The odds ratios for lowest versus highest quartiles were sleep disturbance (OR = 9.7, P = .0095), sleep problems index (SLP)6 (OR = 7.5, P = .032), and SLP9 (OR = 27, P = .0058), which remained significant after controlling for age and number of sedating medications.

Conclusions. Findings from this cross-sectional study, although unable to establish a causal relationship, demonstrate that patients with BMS report a greater degree of sleep problems as compared with controls, and suggest that sleep dysfunction may be a risk factor for BMS and a possible target for treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:203-208)

Burning mouth syndrome (BMS) presents as a chronic burning sensation involving the oral mucous membranes, usually without accompanying clinical and laboratory findings.1,2 In a classic presentation, the burning sensation gradually progresses as the day passes reaching its peak in the late afternoon to early evening. The discomfort may range from minimal to severe and may significantly affect quality of life. Other complaints may be associated with the burning, such as dysgeusia, which supports the designation as a syndrome. In some cases, onset may be associated with an event that is disturbing to the patient. Drug-induced oral symptoms mimicking BMS have been reported in the literature;3 however, in most cases of BMS the etiology is unknown.2 Some studies have identified stress as an etiologic or aggravating factor.2 In addition, clinical responses to low-dose antidepressants and/or antianxiety medications have been reported.2

Disturbance in sleep may cause or aggravate chronic pain. Human experimental studies on sleep deprivation indicate that prolonged periods of sleep disruption induce a state of “heightened vulnerability” to pain, and may produce hyperalgesic states in healthy subjects. Decrease in pressure pain thresholds following decreased total sleep duration, and decrease in heat pain thresholds after overnight sleep deprivation have been demonstrated.4 Sleep deprivation can also have effects, such as mood changes, sleepiness, and fatigue, which might influence pain perception.4 Other chronic pain conditions, including fibromyalgia, have been associated with sleep problems.5,6 Patients with fibromyalgia have been found to have higher occurrence of arousals during night sleep compared with healthy controls and more complaints of insomnia.7

Animal studies have found that sleep deprivation can lower pain thresholds and this effect can be immediate after sleep deprivation and can be prolonged even after restoration of normal sleep.8,9

The role that sleep disturbances play in causation or aggravation of BMS is unknown. We have had some anecdotal reports from patients with BMS that their symptoms worsen when they do not get enough sleep the previous night. Also, some of the medications used to treat BMS may promote sleep.2 Therefore, we hypothesized that sleep-related variables may be associated with BMS. The primary objective of this study was to evaluate a possible association between sleep-related variables and BMS. In addition, we planned to evaluate
the role of sleep-related variables as aggravating factors in patients with preexisting BMS.

METHODS

A case-control study was conducted at the University of California, San Francisco (UCSF). This study was approved by the Institutional Review Board at UCSF, and was registered on http://clinicaltrials.gov identifier: NCT00525421. Twenty-eight cases and 27 controls were enrolled between October 2006 and August 2008. Enrolled patients (but not controls) were followed longitudinally by telephone contact.

Eligibility criteria

Cases were composed of patients diagnosed with BMS at the UCSF Oral Medicine Clinic. The diagnosis of BMS was made when the following 3 criteria were met: (1) the symptoms included a complaint of a burning sensation involving the oral mucosa in part or whole, with or without associated symptoms, such as altered taste; (2) normal oral mucosal examinations; and (3) exclusion of local or systemic factors that may cause similar symptoms. This was done by patient history, review of recent laboratory tests, and oral examinations to rule out anemia, uncontrolled diabetes, thyroid imbalance, or xerostomia-related symptoms.

Controls included patients with leukoplakia, pigmented lesions, traumatic lesions, aphthous ulcers, reticular oral lichen planus, benign tumors, mucoceles, and pemphigoid matched on age (±5 years) and gender to the cases. New patients as well as those presenting for follow-up visits were eligible.

Exclusion criteria included age younger than 18 years, pregnancy, and systemic corticosteroid therapy within the previous 2 weeks, because of the possible effect on sleep patterns. Written consent was obtained from all participants. A consecutive sample of eligible patients was enrolled into the study. Subject enrollment and follow-up are outlined in Fig. 1.

Data collection

At the time of enrollment, each case and control participant was administered the following 2 questionnaires by interview: (1) an enrollment questionnaire with demographic information and medication use, and (2) a numerical rating scale (NRS) for measurement of oral symptoms. This scale ranged from 0 to 10 (0 = no discomfort and 10 = worst imaginable discomfort).

In addition, the following 2 self-administered questionnaires were completed by the participants: (1) sleep scale from the medical outcomes study (MOS), and (2) current sleep status scale (hours of sleep attained the previous night and the night before). The questionnaires were reviewed for completeness before collection.

BMS patients were followed by telephone contact or e-mail once per month for the following 6 months and a subset of the questions on the MOS sleep scale, medication use, NRS, and the current sleep status scale were administered by interview.

Generation of MOS sleep subscales

Items on the MOS sleep scale were averaged to generate subscales as per the MOS sleep scale user’s manual: (1) sleep disturbance-SLPD4 (4 items: measures the ability to fall asleep and maintain restful sleep); (2) Sleep adequacy-SLPA2 (2 items: measures the sufficiency of sleep, ie, sleeping enough to provide restoration of wakefulness); (3) sleep somnolence-SLPS3 (3 items: measures daytime drowsiness); (4) sleep problems index 1-SLP6 (6 items: provides a summary of sleep problems and contains questions from the sleep disturbance, sleep adequacy, respiratory impairment, and somnolence domains); and (5) sleep problems index 2-SLP9 (9 items: provides a more comprehensive summary than the SLP6; the 3 questions in addition to those in the SLP6 measure time to fall asleep, feeling that sleep was quiet, and feeling drowsy during the day).

Statistical methods

Descriptive statistics, including means, standard deviations, medians, minimum, maximum, and percentages were used to summarize all variables. Comparisons of BMS cases and controls were made using the Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Logistic regression models were used to examine the association of MOS subscale responses and other factors with BMS. Factors were evaluated in both unadjusted models and models controlling for age and sedating medications. To investigate the relationship between increasing values (quartiles) of sleep...
subscales and risk of BMS, the Cochran-Armitage trend test was used to assess the underlying trend.

Among BMS patients only, the relationship between NRS severity and MOS subscale responses was investigated by first examining correlations and then performing multivariate linear regression of NRS with each subscale predictor modeled separately, adjusting for age, sex, and sedating medications. Longitudinal analysis was conducted to address whether NRS (severity) varies with changes in sleep over time in patients with BMS. The MOS subscale responses at each visit were included as predictors in models of NRS (severity) over time, adjusted for date of visit and sedating medications. Because measurements were taken on the same subjects at different visits, they are likely correlated. To accommodate this correlation, mixed model regression was used with a random subject effect. Unlike repeated measures analysis of variance (ANOVA), mixed model regression also allows for unbalanced data, use of all available data when some are missing, and can incorporate predictors that change from one time to the next.13

For both linear regression and linear mixed models, the residuals were used to assess the assumption of normally distributed errors. Linearity assumptions of continuous predictors were assessed by checking the need for quadratic terms. Analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC).

CASE-CONTROL ANALYSES
Comparison of cases and controls: Baseline characteristics and sleep variables

Table I shows values for baseline characteristics and sleep variables for the case and the control group. Age and number of current medications (sedating, stimulating, other) were similar between the 2 groups. Statistically significant differences were found in the following (mean [SD] for cases versus controls): SLPD4 (41.3 [23.3] versus 25.4 [20.4], \( P = .0067 \)), “Awaken short of breath or with headache (SLP-
Evaluation of sleep dysfunction as a risk factor for burning mouth syndrome

Table II shows the results of the logistic regression analyses with case versus control status as the outcome and each of the sleep subscales as independent variables (categorized as quartiles) in separate models. Each model controlled for age and sedating medications. The odds ratios (both adjusted and unadjusted) for SLPD4, SLP6, and SLP9 were statistically significant, as were the P values for trend, indicating a dose response with an increasing risk for BMS with increasing values of these sleep subscales.

CASES ONLY

Cross-sectional analysis: Association of severity of BMS with severity of sleep dysfunction at baseline

We evaluated whether severity of BMS (NRS scores) correlated with severity of each sleep subscale at baseline. Linear regression coefficients for NRS with each of the sleep subscales, and results from multiple regression analysis controlling for age, sex, and sedating medications.
medications, are presented in Table III. Only SLPSOB1 scores were associated (positively) with NRS scores at baseline. In addition, participants with optimal sleep dichotomy (SLPOP1) at baseline had a mean NRS score 2.2 U higher than participants without optimal sleep dichotomy ($P = .02$); however, after controlling for age, sex, and number of sedating medications, this difference was not statistically significant.

**Longitudinal analysis: Correlation of severity of BMS with severity of sleep dysfunction over time**

We evaluated whether severity of BMS (NRS scores) varies with sleep subscale scores over time, controlling for use of sedating medications. The results are presented in Table IV. In a linear mixed model controlling for time and sedating medications, severity of BMS (NRS scores) was positively associated with SLPSOB1 scores ($P = .0031$) after adjusting for number of sedating medications used. None of the other sleep subscales showed an association over time with NRS scores.

This is the first study to demonstrate a strong association between sleep variables (sleep disturbance and sleep problems indexes from the MOS sleep scale) and BMS.

We measured the possible confounders of age, gender, and use of sedating medications, and found strong associations between sleep variables and BMS even after statistically adjusting for these variables. However, stress, depression, and other psychological factors, which may be along the etiologic pathway or alternatively could be confounders were not measured and could not be evaluated or adjusted for in the analyses. Furthermore, although the strength of association seen between the sleep variables and BMS is striking, the casual association of sleep variables as risk factors for BMS cannot be confirmed by these results, nor can it be elucidated whether it is the sleep variables affecting BMS or vice-versa, in part because of the cross-sectional nature of the study design.

**DISCUSSION**

In our study (in cases only), the association of BMS severity and sleep variable severity at baseline and over time was evaluated to study the role of sleep dysfunction as an aggravating factor in patients with preexisting BMS. We did not find statistically significant associations except for SLPSOB1 (Tables III and IV). A major limitation of these cross-sectional and longitudinal analyses limited to cases, was the lack of power. We had a sample size of 28 cases at baseline, and, in addition, loss to follow-up was high, further decreasing the power in the longitudinal analyses. The question

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**Table III.** Linear regression coefficients for NRS with each of the sleep subscales, and results from multiple regression analysis controlling for age, sex, and sedating medications (cases only, cross-sectional analysis, $n = 28$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted coefficient</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>$P$ value</th>
<th>Adjusted coefficient*</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLPD4</td>
<td>-0.002</td>
<td>-0.043</td>
<td>0.040</td>
<td>.940</td>
<td>0.007</td>
<td>-0.032</td>
<td>0.046</td>
<td>.720</td>
</tr>
<tr>
<td>SLPSNR1</td>
<td>-0.014</td>
<td>-0.044</td>
<td>0.016</td>
<td>.350</td>
<td>0.000</td>
<td>-0.033</td>
<td>0.033</td>
<td>.990</td>
</tr>
<tr>
<td>SLPSOB1</td>
<td>0.043</td>
<td>0.006</td>
<td>0.081</td>
<td>.027</td>
<td>0.041</td>
<td>0.008</td>
<td>0.074</td>
<td>.017</td>
</tr>
<tr>
<td>SLPA2</td>
<td>0.021</td>
<td>-0.014</td>
<td>0.057</td>
<td>.230</td>
<td>0.008</td>
<td>-0.025</td>
<td>0.040</td>
<td>.630</td>
</tr>
<tr>
<td>SLPS3</td>
<td>0.001</td>
<td>-0.042</td>
<td>0.044</td>
<td>.960</td>
<td>0.002</td>
<td>-0.044</td>
<td>0.049</td>
<td>.910</td>
</tr>
<tr>
<td>SLP6</td>
<td>0.008</td>
<td>-0.048</td>
<td>0.064</td>
<td>.770</td>
<td>0.018</td>
<td>-0.032</td>
<td>0.068</td>
<td>.470</td>
</tr>
<tr>
<td>SLP9</td>
<td>-0.001</td>
<td>-0.058</td>
<td>0.056</td>
<td>.970</td>
<td>0.015</td>
<td>-0.038</td>
<td>0.069</td>
<td>.560</td>
</tr>
<tr>
<td>SLPQRaw</td>
<td>0.302</td>
<td>-0.136</td>
<td>0.740</td>
<td>.170</td>
<td>0.217</td>
<td>-0.226</td>
<td>0.659</td>
<td>.320</td>
</tr>
<tr>
<td>SLPOP1 (yes vs no)</td>
<td>2.200</td>
<td>0.376</td>
<td>4.000</td>
<td>.020</td>
<td>1.248</td>
<td>-0.640</td>
<td>3.100</td>
<td>.180</td>
</tr>
</tbody>
</table>

CI, confidence interval. For other abbreviations, see Table I, recoded variables.

*All models adjusted for age, sex, and number of sedating medications.

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**Table IV.** Results of mixed models* of NRS severity among BMS patients (cases only, longitudinal analysis, n subjects = 28, n observations = 84)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLPD4</td>
<td>0.008</td>
<td>-0.02</td>
<td>0.03</td>
<td>.53</td>
</tr>
<tr>
<td>SLPSNR1</td>
<td>0.011</td>
<td>-0.01</td>
<td>0.04</td>
<td>.37</td>
</tr>
<tr>
<td>SLPSOB1</td>
<td>0.049</td>
<td>0.02</td>
<td>0.08</td>
<td>.0031</td>
</tr>
<tr>
<td>SLPA2</td>
<td>0.014</td>
<td>-0.01</td>
<td>0.04</td>
<td>.25</td>
</tr>
<tr>
<td>SLPS3</td>
<td>0.021</td>
<td>-0.01</td>
<td>0.05</td>
<td>.19</td>
</tr>
<tr>
<td>SLP6</td>
<td>0.013</td>
<td>-0.02</td>
<td>0.04</td>
<td>.42</td>
</tr>
<tr>
<td>SLP9</td>
<td>0.016</td>
<td>-0.02</td>
<td>0.05</td>
<td>.33</td>
</tr>
<tr>
<td>SLPQRaw</td>
<td>0.107</td>
<td>-0.05</td>
<td>0.27</td>
<td>.18</td>
</tr>
</tbody>
</table>

BMS, burning mouth syndrome; CI, confidence interval; NRS, numerical rating scale. For other abbreviations, see Table I, recoded variables.

*All models have random subject effect and are adjusted for visit date and number of sedating medications.
SLPSOB1 inquires about waking up either short of breath or with a headache. This may be a true association indicating that BMS severity is positively correlated with SLPSOB1 (one measure of sleep dysfunction) at a point in time and longitudinally over time. However, an alternative explanation is that participants may have included discomfort from headaches into the score for BMS severity, which may explain this positive correlation.

Treatment of BMS includes the administration of low doses of benzodiazepines, including clonazepam, and chlordiazepoxide or tricyclic antidepressants, such as amitriptyline. The mechanism of action of these drugs in BMS is unknown. However, it is known that these medications have an effect on sleep and have also been used in treatment of insomnia.

It is possible that this effect on promoting sleep may partially explain the mechanism of action of these drugs in BMS.

The results from this study suggest a new direction for etiologic and interventional research in BMS. Larger prospective studies of this association are needed to add to our knowledge of the causative role of sleep in BMS. In addition, both pharmacologic and especially nonpharmacologic approaches, which have fewer side effects, to improving sleep quality could be evaluated as interventions for BMS.

In conclusion, the findings from this case-control study, although unable to establish a causal relationship, demonstrate that patients with BMS report a greater degree of sleep disturbance and sleep problems as compared with controls, and suggest that sleep dysfunction may be a risk factor for BMS and a possible target for treatment.

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REFERENCES


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