A Qualitative Systematic Review of the Association of Sleep Disturbances with Burning Mouth Syndrome: An Overlooked Relationship

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Abstract

Objectives: To review the relevant literature to assess if patients with burning mouth syndrome (BMS) are more prone to have sleep disturbances than general population.

Methods: The literature search for relevant articles was from July 2020 to March 2021. A systematic search of PubMed, Embase, Google Scholar, Cochrane library, Dentistry & Oral Sciences Source, and Scopus was conducted to search for relevant studies. The quality of studies was assessed in accordance with the Joanna Briggs Institute's guidelines and using the software SUMARI – The System for the Unified Management, Assessment and Review of Information. Confidence in the findings was assessed using the GRADE-CERQual approach.

Results: A total of 1064 studies were initially identified from the search; 6 studies, two cross-sectional and 4 case controls, met the inclusion criteria and were selected for this systematic review. Sleep disturbances was a required outcome measured in selected studies evaluating symptoms of BMS. For studies that were included in the final analyses, BMS was found to relate to several dimensions of sleep including sleep disturbance and duration (n=6), sleep affecting day-time function (n=4), sleep quality (n=6), sleep efficiency (n=4), and ability to fall asleep (n=4). Consistent evidence of moderate confidence found that BMS was associated with greater sleep disturbance, reduced sleep quality, increased time taken to fall asleep, reduced sleep efficiency, and poor day-time function. Whereas evidence of low confidence was found regarding the association of BMS with reduced sleep duration.

Conclusions: Although the presented studies could not establish a direct causal relationship between BMS and sleep disturbances, it revealed that sleep disturbance can be a risk factor or/and an aggravator of BMS symptoms. Medications and psychological management strategies to improve sleep may be considered in future research for managing BMS patients.

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Introduction
Burning mouth syndrome (BMS), also known as glossodynia, glossalgia, stomatodynia, stomatopyresis are all terms used to describe chronic pain disorder of unknown etiology that frequently affects postmenopausal women and it is characterized by a burning sensation of the oral cavity in the absence of any identifiable organic disease (1). The etiology of primary BMS is unknown but recent neurophysiological, psychophysical, neuropathological and brain imaging studies using recent diagnostic criteria have resulted in advances in the understanding of the condition’s pathophysiology. There is growing evidence that primary BMS is of neuropathic origin but there is still a small percentage of BMS patients who exhibit no abnormalities in neurophysiologic and Quantitative Sensory Testing (QST) measurements. BMS can be classified into primary or secondary based on etiology but, to date, this classification has not been validated (2) and BMS remains a challenging diagnosis of exclusion. Secondary causes of pain of the oral mucosa that is caused by local or systemic pathologies such as deficiencies in iron or diabetes should be excluded to give the diagnosis of primary BMS (3). The evidence also shows that due to variable diagnostic criteria, the prevalence of BMS occurs between 0.7% and 15% affecting mainly postmenopausal females with male-to-female ratio of 1:5 to 1:7 (1). Moreover, prevalence in both males and females seems to increases with age (1). To date, there is no cure for BMS and there is no standard algorithm for management. Despite the fact that most cases of BMS appear not to be associated with evident organic changes, or direct risks to health, BMS can significantly reduce the quality of life for such patients. Yet, as with all chronic diseases, both physical and psychological comorbidities occur and should be investigated. Although the
relationship between BMS and depression and anxiety are well documented in the literature, little is known about the relationship between BMS and sleep disturbances and whether improvement of sleep quality will improve symptoms of BMS. As most orofacial pain and oral medicine specialists often overlook the role of sleep in the genesis and aggravation of BMS symptoms, the present systematic review seeks to evaluate the relationship of sleep disturbances with BMS as an important diagnostic component. If such a relationship exists, sleep-promoting medications and other sleep improving strategies may be of help in the management of BMS patients. Although the current literature establishes a significant relationship between chronic pain and sleep disturbances, the association of BMS and sleep is not well studied. Thus, the objective of this review was to evaluate if patients with BMS are more prone to have sleep disturbances that needs to be addressed by clinicians to improve treatment outcomes and overall quality of life of affected individuals.

Materials and Methods
We performed a systematic review of the literature evaluating the association between sleep disturbance and BMS. The search included studies with different methodologies including observational studies, such as cross-sectional and case control studies that were selected according to the criteria outlined below. The main outcome was to determine if patients with BMS report more sleep disturbances than general population. This review considered studies of English literature published before March 2021, reporting the relationship between BMS and sleep, or BMS studies where sleep was an outcome measure. Studies who enrolled subjects with the following
criteria were included: adult human males and females, aged 18 years or older and subjects who had a diagnosis of primary BMS without previous diagnosis of sleep disorders.

The proposed systematic review was conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of qualitative evidence (1) and has been registered with (PROSPERO), International Prospective Register of Systematic Reviews (CRD 42020202650). This review comprised 3 phases. **Phase 1** involved a systematic search of the literature based on a combination of keywords (see section Phase 1: Database Search). **Phase 2** involved screening of literature titles and abstracts using specific inclusion criteria (see inclusion criteria for systematic review), and full article screening. Finally, **Phase 3** involved classifying the internal validity (quality) of the included studies using established and valid tools, extraction of data from selected studies, and synthesis of the evidence.

**Phase 1: Search Strategy**

The search strategy aimed to find published studies of qualitative and quantitative methods. However, only the qualitative data from mixed-methods studies were used in the data analysis. The search strategy was undertaken in Google Scholar, Cochrane library, Dentistry & Oral Sciences Source, MEDLINE (PubMed), Scopus (Elsevier), and Embase (Ovid). All identified keywords and index terms were adapted for each included information source. Databases were searched for relevant English language articles published from July 2020 to March 2021. Finally, the reference lists of all studies selected for critical appraisal were screened for additional studies. The main search strategies are provided in Appendix I.
Phase 2: Study selection

Following the search, all identified citations collated and uploaded into EndNote X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts were screened by two independent reviewers (FA and LG) for assessment against the inclusion criteria defined for the review. Studies that met the inclusion criteria were retrieved in full and their details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia) (5). The full text of selected studies was retrieved and assessed in detail against the inclusion criteria by two independent reviewers (FA and EK). Full-text studies that did not meet the inclusion criteria were excluded, and reasons for exclusion were reported in the systematic review. The results of the search were presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (*2) (Figure 1). Any disagreements that arose between the reviewers were resolved through discussion.

Phase 3: Assessment of methodological quality and strength of evidence

Quality of the studies was assessed in accordance with the Joanna Briggs Institute (JBI) guidelines. Two independent reviewers (FA and EK) utilized the JBI System for the Unified Management, Assessment and Review of Information (SUMARI)(5). Any disagreements between the reviewers were resolved through discussion or with a third reviewer (LG). Following critical analysis, studies that did not meet a certain quality threshold were excluded. The decision to exclude was based on cut-off scores of less than 70% of the items assessed for all JBI critical appraisal tools. This represents the following checklist amount of “yes” answers: fewer than seven out of 10 for case-control studies and fewer than five out of
eight for analytical cross-sectional studies. The results of critical appraisal were reported in (Table 2).

Data extraction

Data extracted from studies were included in the review using the standardized Joanna Briggs Institute data extraction tool. The data extracted include specific details about the authors, year of study enrolment, country of origin, outcome analysed in the individual studies, details about populations, study methods and interventions. Findings, and their illustrations, were extracted and assigned a level of credibility (Table 3&4).

Data Synthesis

Qualitative research findings were pooled using the meta-aggregation approach. Thematic analysis was used to synthesize findings and a narrative approach was used to present findings in accordance with the JBI guidelines using the Joanna Briggs Institute’s guidelines and using the software SUMARI – The System for the Unified Management, Assessment and Review of Information. Only unequivocal and credible findings were included in the synthesis. The results of qualitative synthesis were presented in a narrative form including tables and figures (Table 3) and (Figure 2) to aid in data presentation.

Assessing confidence in the findings

The final synthesized findings were graded according to the GRADE-CERQual approach (6) by two independent reviewers (FA and LG) for establishing confidence in the output of qualitative research synthesis and presented in a Summary of Findings (Table 1). The Summary of Findings includes the major elements of the review and details how the GRADE-CERQual score was
developed. Included in the table is the title, population, phenomena of interest, and context for the specific review. Each synthesized finding from the review is presented, along with the type of research informing it, scores for methodological limitations, coherence, relevance, adequacy, and the overall GRADE-CERQual score.

**Results**

*Study inclusion*

From a total of 1064 database hits, six studies of various methodologies fulfilled the inclusion criteria for this review: two cross-sectional studies and four case-controlled studies. The remaining of the studies were excluded, and reasons of exclusion were reported in the PRISMA flow chart (Figure 1). A total of six articles underwent quality assessment, and no articles were excluded following assessment of methodological quality. A final total of six studies was included in the review.

*Methodological quality*

All six studies included are observational studies. Two were cross-sectional studies (7) and (8), and four were case-control studies (9), (10), (11) and (12). Overall, the methodological quality of included studies was considered good and there were no studies that were excluded following critical appraisal when assessed using the standard Joanna Briggs Institute Critical Appraisal Checklist for Qualitative Research using JBI (SUMARI). (Table 2).
**Characteristics of included studies**

The included studies were conducted between 2013 and 2019. Two were cross-sectional studies undertaken in Spain (7) and South Korea (8). Four were case controls studies undertaken in Naples (9), Italy (10), Korea (11), and Iran (12). All studies used qualitative descriptive methodologies to assess sleep disturbances in patients diagnosed with BMS. Data collection was based on self-reported validated sleep questionnaires given to patients attending oral medicine clinics. All the six included studies used The Pittsburgh Sleep Quality index (PSQI) and four of these studies used The Epworth Sleepiness Scale (ESS) in addition to the PSQI. Patients from both control and study groups were matched for sex and gender in all studies except in two studies that had more female patients (10) and (8). All studies recruited patients from single university oral medicine clinics setting except one that was undertaken in ten oral medicine units of different universities across the country (10). The BMS group inclusion criteria in all included studies was in accordance with the International Classification of Headaches (13) and the total number of participants drawn from the included studies was 856. Table 4 outlines the characteristics of included studies.

**Review findings**

The review included six studies to evaluate if patients with BMS are more prone to have sleep disturbances. In the selected studies, the dimensions of sleep were assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI is a self-reported questionnaire (subjective) consisting of 19 questions correlating to seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of
sleep medication and daytime dysfunction. Each domain is given a direct score of 0–3. A score of zero indicates no problem in this domain, while three indicates a serious problem. The sum of the seven scores gives an overall score of 0–21. A PSQI total of <5 is the threshold for subjects classified as satisfactory sleepers, while a patient with a score of >5 can be considered as suffering sleep disturbance (14). The Epworth daytime sleepiness scale (ESS) determines or measures daytime sleepiness by means of eight items. The subject is questioned as to the frequency (or probability) of falling asleep on a scale of 1–3 in eight different situations that most people experience in daily life such as sitting and reading, watching TV, sitting, inactive in public place, as a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quietly after a lunch without alcohol, in a car, while stopped for a few minutes in the traffic. The eight items are totaled to give an overall score of 0–24, with higher scores indicating greater sleepiness during common daily activities. A score of 0–9 is considered normal, A score of 11–15 indicates the possibility of slight to moderate sleep apnea, while a score of over 16 indicates severe sleep apnea or narcolepsy (15). The assessment of the dimensions of sleep affected resulted in six synthesized findings: 1) BMS patients have more rates of sleep disturbance than controls; 2) BMS patients have less sleep duration rates than controls; 3) BMS patients have higher rates of daytime dysfunction than controls; 4) BMS patients have lower sleep quality than controls; 5) BMS patients have more difficulty falling asleep than controls; and 6) BMS patients have lower sleep efficiency than controls. The six synthesized findings were rated using the GRADE-CERQual approach (6).
**Synthesized finding 1:** *BMS patients have more rates of sleep disturbance than controls*

Six studies used (PSQI) to assess sleep disturbance and duration (7), (8), (9), (10), (11), and (12). Outcome consistent evidence from above six studies of (moderate confidence of evidence) found that BMS patients have significantly higher rates of sleep disturbance than controls.

**Synthesized finding 2:** *BMS patients have less sleep duration rates than controls*

Two of the included studies, (8) and (10) found significantly lower rates of sleep duration in BMS patients compared to controls (low confidence level of evidence).

**Synthesized finding 3:** *BMS patients have higher rates of daytime dysfunction than controls*

Of the six studies used (PSQI) and four studies used (ESS), four reported daytime dysfunctions in the BMS groups using PSQI questionnaire (10), (8) (9) (11). Four studies reported significantly more daytime dysfunction in BMS group using ESS scale (7), (9), (10), and (11). Outcome Consistent evidence from five (moderate confidence level of evidence) studies found that poor sleep was adversely associated with day-time function in BMS patients.

**Synthesized finding 4:** *BMS patients have lower sleep quality than controls*

Six studies used (PSQI) to subjectively measure sleep quality. All these six studies (moderate confidence level of evidence) showed significantly low sleep quality in BMS groups when compared to controls (9), (10), (11), (12), (8), and (7).
Synthesized finding 5: BMS patients have more difficulty falling asleep than controls
Six studies (moderate confidence level of evidence) used (PSQI) to measure sleep latency and four concluded that BMS patients have significant difficulty in falling asleep when compared to controls (7), (9), (10), and (8).

Synthesized finding 6: BMS patients have lower sleep efficiency than controls
Six studies (moderate confidence level of evidence) used (PSQI) to measure sleep efficiency, which was significantly lower in the BMS groups in four of these studies (7), (9), (10), and (8).

Summary
Overall, consistent evidence from various (six) studies [moderate confidence level] suggests that BMS patients have greater sleep disturbance compared with controls, and consistent evidence from four studies [moderate confidence], found that BMS patients have greater difficulty falling asleep compared with controls. Quality of life and function were also assessed in these studies; and consistent evidence from most studies [moderate confidence] found that poor sleep in BMS patients is associated with poorer day-time function (five studies) and sleep quality (six studies) when compared with controls. Similarly, evidence from four studies [moderate confidence] found that BMS patients suffer from reduced sleep efficiency compared with controls. Lastly, consistent evidence from two studies [low confidence level] found that BMS patients have less sleep duration than controls.
Discussion

This review examined the association between BMS and various dimensions of sleep. Although we only identified 6 studies that fit the search criteria, and variability across studies may limit full assessment for agreement in systematic reviews, in our search most studies were conducted at a single center university based oral medicine clinics, except one study that included multi-oral medicine clinics from 10 universities across the country (10); thus some correlations were found across studies, including similar assessments and scales that were used to measure sleep disturbance. Studies were particularly aged and sex matched, with the exception of two studies that included greater than 75% of female subjects (10)-(8). These findings corroborate with previous reported research in BMS that shows BMS being most prevalent in postmenopausal females.

Overall, there was substantial evidence that BMS is associated with sleep disturbances, but a causal relationship could not be found due to the observational nature of included studies and lack of additional studies designed as controlled, interventional trials. Most of the included studies involved small sample size, and had resource limited settings (e.g., did not represent the general population, presented heterogeneity of study statistical methods and methods of reporting results) which contributed to the lack of stronger evidence. Also, due to the natural absence of randomization and blinding in observational studies and low sample sizes, many studies received a lower confidence in the overall CERQual assessment score. One strength of our findings was the fact that all qualified studies under our criteria used similar pain level and sleep disturbances validated questionnaires. These validated questionnaires allowed for the assessment of several dimensions of “sleep” with results showing that most of
them are found to be impaired in BMS patients when compared with controls (i.e., sleep duration, sleep disturbance, daytime function, sleep quality, and ability to fall asleep and sleep efficiency).

Assessment of sleep can be subjective; for example, the results of valid and reliable questionnaires, such as Pittsburgh Sleep Quality Index (PSQI), reported by patients. Whereas objective assessment of sleep require the use of complex and expensive measures such as polysomnography (PSG), that require the simultaneous assessment of brain activity, eye movement, and muscle activity (4). This review includes only subjective measurements of sleep disturbances in BMS patients and future studies should use objective measurement tools to adjunct the self-reported subjective assessment tools such as use of electronic daily diaries, PSG, and actigraphy to provide an accurate measure of overall sleep disturbance. Such studies would allow for a better understanding of this condition of multifactorial origin that is mostly idiopathic, and its etiopathogenesis remains largely unknown.

Clinically, in patients with BMS, it is often challenging to isolate one etiological factor aggravating symptoms of BMS and it is unclear whether sleep disturbance is a cause, or an effect of chronic pain. This was exemplified in previous studies of BMS where about 23% of chronic pain patients reported at least one insomnia symptom, whereas 40% of insomnia patients reported at least one chronic pain condition (16). Sleep disturbance also can affect individual’s response to pain, and experimentally induced sleep deprivation studies enrolling a healthy pain-free population, has reportedly resulted in heightened pain perception, reduced pain tolerance and pain thresholds (17). In our search, BMS was found to relate to
several dimensions of sleep including sleep disturbance and duration, sleep affecting day-time function, sleep quality, sleep efficiency, and ability to fall asleep. This association was also reported in a retrospective population-based cross-sectional study on 47,941 Taiwanese patients with apnea and non-apnea sleep disorders. This study concluded that poor sleep increases the risk of BMS, indicating the important role of sleep disturbances in BMS (18). Although it is generally assumed that psychosocial comorbidities such as depression and anxiety in BMS patients are the cause of sleep disturbances, recent accumulative evidence implies that primary sleep disorders should be considered as separate comorbidity and treating sleep disturbances can improve quality of life in these patients even in absence of a confirmed diagnosed of depression and/or anxiety (19).

**Conclusion**
Given the disabling nature of BMS, it is of great importance to identify effective methods of treatment. Due to the limited number of controlled clinical trials with low risk of bias, there is lack of evidence to support or refute the use of any interventions in managing BMS as a direct cause of sleep disturbance. Further clinical trials, with standardized methodology and reproducible outcomes are required for better understanding of the etiological and psychological nature of this disorder. This study supports what previous studies had concluded that as with other chronic orofacial pain disorders, BMS patients have an increased risk in developing sleep disturbances than the general population and both subjective and objective sleep assessment tools are needed in future studies to assess such comorbidities and to help in the development of targeted and more precise pharmacological and non-pharmacological interventions for management of this
painful and often frustrating condition. Ultimately, an interdisciplinary and systematic approach is required for diagnosis and management of BMS patients who are mostly treated by oral medicine specialists. Yet these cases should include evaluation of other comorbidities associated with the condition, including sleep disturbances. Medications and other management strategies to improve sleep may also be considered in future research for managing BMS patients. In conclusion, although the presented studies could not establish a causal relationship between BMS and sleep disturbances it shows that patients with BMS have more risk in developing sleep disturbance that in turn can aggravate their symptoms.

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References:


Appendix I:

Search strategy:

PubMed:

((("Hypnotics and Sedatives"[Mesh] OR sedatives OR "sleep medicine" OR "Hypnotics and Sedatives" [Pharmacological Action] OR "GABA Modulators"[Mesh] OR "GABA Modulators" [Pharmacological Action] OR "GABA Plasma Membrane Transport Proteins"[Mesh] OR "Barbiturates"[Mesh] OR sleep OR "Sleep Wake Disorders"[Mesh] OR "Sleep"[Mesh] OR sedative or sedatives OR sleep-wake OR insomnia OR barbiturates OR hypnotic OR GABA ) AND ( "Burning Mouth Syndrome"[Mesh] OR "Burning mouth syndrome- Type 3" [Supplementary Concept] OR glossodynia OR "Stomatodynia"[Supplementary Concept] OR orodynia OR oral dysaesthesia OR glossopyrosis OR stomatodynia OR burning tongue OR stomatopyrosis OR sore tongue OR burning tongue syndrome OR burning mouth OR sore mouth)))

Embase:
(‘hypnotic sedative agent’/exp OR 'sedative agent'/exp OR 'sedative agent'/exp OR 'sleep medicine'/exp OR 'benzodiazepine receptor affecting agent'/exp OR '4 aminobutyric acid carrier'/exp OR 'insomnia'/exp OR 'sleep induction'/exp OR 'sleep disorder'/exp OR 'sleep'/exp OR Sleep OR sedative or sedatives OR sleep-wake OR insomnia OR barbiturates OR hypnotic OR GABA) AND (‘burning mouth syndrome’/exp OR 'glossodynia'/exp OR 'mouth pain'/exp OR glossodynia OR orodynia OR 'oral dysaesthesia' OR glossopyrosis OR stomatodynia OR 'burning tongue' OR stomatopyrosis OR 'sore tongue' OR 'burning tongue syndrome' OR 'burning mouth' OR 'sore mouth' OR Glossalgia)

**Scopus:**

( ( glossodynia OR orodynia OR "oral dysaesthesia" OR glossopyrosis OR stomatodynia OR "burning tongue" OR stomatopyrosis OR "sore tongue" OR "burning mouth" OR "sore mouth" OR Glossalgia ) AND ( Sleep OR sedative or sedatives OR sleep-wake OR insomnia OR barbiturates OR hypnotic OR GABA ))

**Cochrane:**

1. Mesh Description: "Burning Mouth Syndrome"[Mesh] explode all trees
2. Mesh Description: “Glossalgia” [Mesh] explode all trees
3. ( glossodynia OR orodynia OR "oral dysaesthesia" OR glossopyrosis OR stomatodynia OR "burning tongue" OR stomatopyrosis OR "sore tongue" OR "burning mouth" OR "sore mouth" OR Glossalgia) AND ( Sleep OR sedative or sedatives OR sleep-wake OR insomnia OR barbiturates OR hypnotic OR GABA )
4. Mesh Description: "Sleep"[Mesh] explode all trees
5. Mesh Description: "Sleep Wake Disorders"[Mesh] explode all trees
6. Mesh Description: "Hypnotics and Sedatives"[Mesh] explode all trees
7. Mesh Description: "GABA Modulators"[Mesh] explode all trees
8. Mesh Description: "GABA Plasma Membrane Transport Proteins"[Mesh]
9. Mesh Description: "Barbiturates"[Mesh] explode all trees
10. Sleep OR sedative or sedatives OR sleep-wake OR insomnia OR Barbiturates OR hypnotic OR GABA
11. (#1 OR #2 OR #3) AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

Dentistry and Oral Sciences Source:

((DE "SLEEP" OR DE “SLEEP DISORDERS” OR sleep OR sedative or sedatives OR sleep-wake OR insomnia OR Barbiturates OR hypnotic OR GABA ) AND ( Burning mouth OR glossodynia OR DE "BURNING mouth syndrome" OR orodynia OR "oral dysesthesia" OR glossopyrosis OR stomatodynia OR "burning tongue" OR stomatopyrosis OR "sore tongue" OR "burning mouth" OR "sore mouth" OR glossalgia ) )

Appendix II:

Included Studies for the quality assessment:


**Appendix III:**

**Excluded Studies:**


**Other references:**

Available from [https://synthesismanual.jbi.global](https://synthesismanual.jbi.global). [https://doi.org/10.46658/JBIMES-20-01].
