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ORIGINAL ARTICLE

Individual oral symptoms in burning mouth syndrome may be associated differentially with depression and anxiety

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ABSTRACT

Background Burning mouth syndrome (BMS) is an idiopathic disease characterized by the feeling of burning in the oral cavity. Ten per cent of patients presenting to oral medicine clinics have BMS. Anxiety and depression are common co-morbidities in BMS, but it is not known if they are associated with specific BMS symptoms. **Objective** In an exploratory analysis, this study examined the association of generalized anxiety and depression with individual BMS symptoms. **Methods** Forty-one patients were recruited from a dental outpatient clinic (30 with BMS and 11 with other oral conditions), evaluating specific BMS symptoms and their intensity. Anxiety and depression symptoms were assessed using a standardized measure (Clinical Interview Schedule–Revised). **Results** Taste change ($p = 0.007$), fear of serious illness ($p = 0.011$), metallic taste ($p = 0.018$) and sensation of a film on the gums ($p = 0.047$) were associated with an excess of psychiatric symptoms. More specifically, metallic taste (coefficient = 0.497, 95% CI = 0.149–0.845; $p = 0.006$) and sensation of film on gums (coefficient = 0.625, 95% CI = 0.148–1.103; $p = 0.012$) were associated significantly with higher scores for depressive symptoms; taste change (coefficient = 0.269, 95% CI = 0.077–0.461; $p = 0.007$), bad breath (coefficient = 0.273, 95% CI = 0.065–0.482; $p = 0.012$) and fear of serious illness (coefficient = 0.242, 95% CI = 0.036–0.448; $p = 0.023$) were associated with higher anxiety scores. **Conclusion** Specific BMS symptoms are associated differentially with generalized anxiety and depression. Dental practitioners should ascertain which BMS symptoms are predominant and be mindful of the association of certain symptoms with anxiety or depression and, where necessary, consider medical consultation.

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Introduction

Burning mouth syndrome (BMS) is a chronic condition in which patients complain of stinging, itching or burning sensations in the oral cavity in the absence of an organic cause.[1] Several criteria have been developed to facilitate the diagnosis of BMS. Scala et al. [2] proposed one cardinal symptom, pain occurring in the oral mucosa (in the absence of detectable oral lessions), with the following necessary features (Table 1): the pain being a deep burning/tingling or scalding sensation, bilateral, lasting for at least 4–6 months, continuous during the day, with no worsening with eating or drinking and which does not affect sleep. All of these criteria need to be present to make a diagnosis. Some further clinical features, commonly present but not essential to the diagnosis, were also included: dysgeusia (distortion in taste) and/or xerostomia (dry mouth), sensory or chemosensory alterations, mood changes or psychopathological alterations. According to these criteria, psychiatric symptoms can be considered part of BMS, but it is possible to have BMS without the psychiatric manifestations. BMS has been classified as 'primary' or idiopathic when no organic cause is found and 'secondary' when it is the consequence of a local, systemic or metabolic illness. Lamey [3] describes three different sub-types of BMS according to the interference of symptoms with sleep, disregarding one of Scala's criteria. Some authors differentiate between a 'central BMS' where psychiatric symptoms are common and a peripheral BMS caused by local neuropathy and not related to anxiety or depression. In this paper only idiopathic or 'primary' BMS is discussed.

Most BMS sufferers are women, with a male:female ratio of 1:7.[4] BMS peaks in the perimenopausal period where the prevalence reaches 5.5%.[4] In the general population the estimated prevalence is between 0.7–4.6%.[2] Males have a later onset of symptoms than females. In general dental clinics the prevalence of BMS is reported to be 10%. Patients with BMS report higher numbers of medically unexplained symptoms including tinnitus and fibromyalgia compared to controls and patients with other oral pathologies. In a recent study,[5] 91% of patients with BMS reported somatization compared

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Table 1. Burning mouth syndrome criteria.

Cardinal symptom required for diagnosis: Oral pain[a], bilateral, continuous during the day, burning/scalding/tingling, for at least 4–6 months, does not worsen with eating or drinking and does not affect sleep.	Other clinical features: Dysgeusia[a] Xerostomia[a] Sensory or chemosensory alterations Mood changes/ Psychopathological alterations
No lesions must be detectable in the oral mucosa.	

[a]BMS symptomatic triad. Adapted from Scala et al. [2].

with 1.8% of patients with oral lichen planus. Interestingly, 87% of these somatizations were located in the head and included feeling of lumps in the throat, tinnitus and facial pain.

The prognosis of BMS is poor, with only 3.7% of patients achieving total remission and 28% reporting moderate improvement after 5 years.[6] Several studies have reported an association between BMS and psychiatric comorbidity.[7–11] Taiminen et al.,[12] reported a prevalence of 52.4% of axis I diagnoses (general treatable psychiatric conditions). Almost one third of the patients (30.2%) had major depression, followed by social phobia and specific phobias (15.9% and 11.1%, respectively). In the same study 19% were reported to have axis II diagnoses (personality disorders). Burning mouth syndrome has been associated with generalized anxiety disorder (a type of anxiety characterized by persistent worry and nervousness [13]) and panic disorder.[10] Several authors have noticed increased frequency of cancerphobia (a form of specific phobia) and hypochondriasis.[10]

Aim of study

Since numerous symptoms have been described as being features of burning mouth syndrome, the primary aim of this study was to examine which putative BMS symptoms were associated with symptoms of depression and which with anxiety symptoms. Establishing such links could allow dentists to develop an 'index of suspicion' to focus specifically on depression or anxiety in further questioning. Identification of specific symptoms linked preferentially to generalized anxiety disorder or depression will improve our understanding of the biology of burning mouth syndrome and its association with psychiatric pathologies and will offer guidance regarding specific treatments for the underlying disorders. Although treatments for depression and anxiety disorders may overlap, some medications commonly used in depression have little evidence for efficacy in generalized anxiety disorder and vice-versa. Differentiating whether a patient with BMS has co-morbid depression [13] or generalized anxiety disorder [13] allows treatment for these conditions to be better targeted.

Patients and methods

We studied consecutive patients attending a dental outpatient clinic (oral medicine/oral pathology speciality) at a University Dental Hospital in the UK. All the procedures followed were in accordance with the ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. Ethical approval was obtained from the local research ethics committee (Bath Local Research Ethics Committee, date of issue 5 March 2007, registration number 07/Q2001/41). All potential participants were given written information about the study on attending an oral medicine clinic appointment. Those who decided to take part gave written informed consent at the next appointment in the presence of an investigator (HU or AAK). Participants were categorized based on whether they had a diagnosis of primary burning mouth syndrome (following criteria by Scala et al. [2]) made by a dentist prior to entering the study. Patients had been referred by their local general practitioner or medical specialist who had, in conjunction with the dentist, performed any necessary examinations and appropriate investigations prior to arriving at the diagnosis of idiopathic BMS.

Non-BMS patients attending the same Dental Hospital clinic with non-Burning Mouth Syndrome dental problems (i.e. non-specific oral/dental lesions including lichen planus, hyperplastic gingivae, polyps and aphthous stomatitis, but excluding those with cancers and those with atypical facial pain only) were included for reasons outlined below, but constituted a separate study group.

Thirty subjects with burning mouth syndrome (27 female, mean age = 61.1 years) and 11 participants (nine female, mean age = 58.5 year.) attending the oral medicine clinic with other syndromes (lichen planus $n = 7$, hyperplastic gingivae $n = 1$, polyps $n = 1$, aphthous stomatitis $n = 1$, other $n = 1$) were recruited. The two groups did not differ significantly in the proportion of females (90% vs 82%), nor in age, smoking status (2 vs 1) or presence of a dental prosthesis (3 vs 2). Participants with burning mouth syndrome were more frequently taking both psychotropic (9 vs 0) and non-psychotropic drugs (21 vs 11), but the difference did not reach statistical significance. Patients with BMS prescribed psychotropic drugs were taking tricyclic antidepressants (nortriptyline $n = 3$, amitriptyline, $n = 1$), an SSRI (citalopram $n = 1$), benzodiazepines diazepam and temazepam in combination ($n = 1$), zopiclone ($n = 1$), gabapentin ($n = 1$), flupentixol ($n = 1$) and tryptophan ($n = 1$).

Instruments

At the time the study was designed we were unable to identify a suitable validated questionnaire for self-administration which allowed the presence and intensity of burning mouth syndrome symptoms in the past month to be quantified. We, therefore, formulated a composite questionnaire based on a search of existing literature, documenting the presence and intensity of dental and associated symptoms put forward as being features of Burning Mouth Syndrome. The symptoms included were as follows: (1) Burning in the mouth, (2) Soreness in the mouth, (3) Stinging in the mouth, (4) Dry mouth, (5) Numbness in the mouth, (6) Tingling in the mouth, (7) Changes in taste, (8) Teeth clenching, (9) Tongue thrusting around, (10) Sensation of film on teeth or gums, (11) Metallic or acidic taste, (12) Unpleasant taste, (13) Difficulty eating spicy or acidic foods, (14) Sensation of having cuts in the gums, (15) Bad breath and (16) Fear of having a

serious medical illness. Each question was presented with a visual analogue scale, with the participant rating symptom intensity from 0–9.

In addition to this questionnaire, participants completed the clinical interview schedule–revised (CIS-R) [14] for psychiatric morbidity and additional questions on demographics, smoking and medication. In the PROQSY format, the CIS-R is administered as a computer-based questionnaire which prompts the operator to answer questions on common psychiatric problems. It can be used to generate continuous scores for depression and anxiety symptoms and a total CIS-R psychiatric symptom score. The symptoms contributing to the anxiety score are worry, anxiety, phobia and panic. The total psychiatric symptom score includes not only the core anxiety and depression symptoms, but also related symptoms such as fatigue and obsessionality. The CIS-R instrument may also be used to generate ICD-10 based diagnostic information on individual anxiety disorders using an algorithmic approach based on the data provided.

Statistical analysis

Statistical analyses were run using STATA version 13.[15] In comparing demographic and clinical data between participants with burning mouth syndrome and those with other dental diagnoses, we used Student's T-test for continuous data and Chi-square tests or Fisher's exact tests (where cell values of 5 or less existed) for discrete data. For one comparison, we employed Fisher's exact test despite there being a cell value of zero, which some authors regard as controversial.[16] As a first step in the analysis we examined the ability of the BMS questionnaire's individual symptoms to differentiate participants with a diagnosis of burning mouth syndrome from those with other dental diagnoses. Linear regression was used to examine the association of the burning mouth syndrome diagnosis (as exposure) with each of the above oral symptoms in turn (as outcome) adjusting for age and sex. For each symptom a regression coefficient was calculated, which indicated the magnitude of excess symptom intensity in participants with BMS vs those with other diagnoses, thereby indicating which of the putative BMS symptoms in our questionnaire were most associated with the diagnosis of BMS.

In our primary analysis, we examined the association of oral symptoms with outcome measures generated from the CIS-R by linear regression (total psychiatric morbidity scores, depressive symptom scores and anxiety symptom scores) adjusting for age, sex and diagnosis of BMS in the sample of all participants entering the study. *P*-values were considered significant if $p < 0.05$. The effect of adding smoking to these models was examined. Where indicated, regressions were repeated, adding a further covariate denoting use of specific psychotropic medications, as this was considered a potential confounder in the relation of some BMS symptoms (e.g. dry mouth, a common side-effect of tricyclic antidepressants) and psychiatric morbidity. Finally, the analyses with outcomes of depressive symptom scores and anxiety symptom scores were repeated, restricting the samples to the participants with burning mouth syndrome only and excluding those with other diagnoses.

Results

Participants with BMS had higher scores than those with other diagnoses on the CIS-R for total psychiatric morbidity (6.76 vs 1.63, difference = 5.12, 95% CI = 0.09–10.16, $p = 0.046$). For both depressive and anxiety symptoms, participants with BMS recorded higher scores on the CIS-R than did those with other diagnoses, but the differences were not statistically significant (for depressive symptoms; 3.38 vs 1.00; difference = 2.38, 95% CI = −0.22 to 4.98, $p = 0.072$ and for anxiety symptoms; 1.31 vs 0.55; difference = 0.76, 95% CI = −0.66 to 2.19, NS). Four subjects with BMS, but none of those with other diagnoses, met criteria for generalized anxiety disorder using the CIS-R's ICD-10 based diagnostic algorithms. Symptoms typical of generalized anxiety disorder dominated the anxiety measure employed, with 'anxiety' and 'worry' accounting for 89% of points scored, whereas 'phobia' accounted for 7% and 'panic' 4%. No participant reported panic, phobia or other anxiety symptoms to a degree which led the CIS-R algorithms to suggest the presence of another diagnosable co-morbid anxiety disorder.

Individual symptoms in subjects with BMS vs those with other diagnoses (Table 2)

In linear regression adjusted for age and sex (Table 2), symptoms of burning (regression coefficient for subjects with BMS vs those with other diagnoses = 5.85, $p < 0.001$), dry mouth (coefficient = 4.10, $p = 0.001$), fear of serious illness (coefficient = 2.63, $p = 0.015$), and stinging (coefficient = 2.39, $p = 0.040$) were significantly associated with burning mouth syndrome, while scores for tingling (coefficient = 1.95, $p = 0.060$), metallic or acidic taste (coefficient = 2.16, $p = 0.69$) and teeth clenching (coefficient = 1.75, $p = 0.072$) were appreciably higher in the BMS group (as indicated by the coefficients and the lower 95% confidence limits of the difference between groups being close to zero), but the difference did not reach statistical significance. For the remaining nine putative BMS symptoms, regression coefficients were substantially smaller and there was no significant difference in intensity between participants with a BMS diagnosis and those with other diagnoses.

Table 2. Association of diagnosis of burning mouth syndrome with oral symptom intensity (analysis is linear regression adjusted for age and sex). Regression coefficient indicates magnitude of excess symptom intensity on a scale of 0–9 in participants with BMS ($n = 30$) vs Participants with other dental diagnoses ($n = 11$).

Symptom	Regression coefficient	95% CI	*p*-value
Burning in mouth	5.54	(3.78 to 7.30)	<0.001
Dry mouth	3.91	(1.82 to 5.99)	0.001
Fear of serious illness	2.85	(0.58 to 5.13)	0.015
Stinging in mouth	2.39	(0.12 to 4.67)	0.040
Metallic or acidic taste	2.16	(−0.18 to 4.49)	0.069 (NS)
Tingling in mouth	1.95	(−0.08 to 3.99)	0.060 (NS)
Teeth clenching	1.75	(−0.16 to 3.66)	0.072 (NS)

NS, not significant; *p*-values stated where $p < 0.1$. Relationships between the remaining putative BMS symptoms (taste changes, unpleasant taste, film on teeth/gums, tongue thrusting, soreness in mouth, numbness in mouth, difficulty eating spicy/acidic foods, sensation of cuts in gums and bad breath) and diagnosis of BMS are not tabulated as *p*-values were $p > 0.1$.

Table 3. Association of CIS-R scores (total psychiatric morbidity, depression and anxiety) with oral symptom intensity (tabulation of regression coefficients and *p*-values) in the whole sample ($n = 41$). Analysis is linear regression adjusted for age, sex and diagnosis of burning mouth syndrome. Note that the regression coefficient represents the expected increase in the CIS-R outcome variable for each unit increase in the oral symptom score.

	CIS-R Total	Depression	Anxiety
Burning in mouth	0.558 (NS)	0.129 (NS)	0.264 (NS, $p = 0.054$)
Dry mouth	0.754 (NS, $p = 0.065$)	0.360 (NS, $p = 0.087$)	0.104 (NS)
Fear of serious illness	*0.939* ($p = 0.011$)	0.309 (NS)	*0.241* ($p = 0.023$)
Metallic or acidic taste	*0.850* ($p = 0.018$)	*0.497* ($p = 0.006$)	0.191 (NS, $p = 0.066$)
Taste changes	*0.944* ($p = 0.007$)	0.314 (NS, $p = 0.084$)	*0.269* ($p = 0.007$)
Unpleasant taste	0.696 (NS)	0.291 (NS)	0.236 (NS, $p = 0.053$)
Film on teeth/gums	*1.004* ($p = 0.047$)	*0.625* ($p = 0.012$)	0.258 (NS, $p = 0.075$)
Bad breath	0.720 (NS, $p = 0.063$)	0.282 (NS)	*0.273* ($p = 0.012$)

Significant results ($p < 0.05$) are in italics.

NS, not significant, *p*-value stated where $p < 0.1$. Relationships between the remaining putative BMS symptoms (stinging in mouth, tingling in mouth, teeth clenching, tongue thrusting, soreness in mouth, numbness in mouth, difficulty eating spicy/acidic foods and sensation of cuts in gums) and psychiatric outcome measures are not tabulated as there were no significant associations and all *p*-values were $p > 0.1$.

Individual BMS symptoms and psychiatric morbidity (Table 3)

On linear regression undertaken in the whole sample of 41 participants, with total CIS-R psychiatric symptom score as outcome, adjusted for age, sex and BMS diagnosis, some BMS symptoms (Table 3), notably taste change ($p = 0.007$), fear of serious illness ($p = 0.011$), metallic or acidic taste ($p = 0.018$) and sensation of a film on the gums ($p = 0.047$), were significantly associated with an excess of psychiatric symptoms.

More specifically, depressive symptom scores were associated significantly with metallic or acidic taste (coefficient = 0.497, 95% CI = 0.149–0.845; $p = 0.007$) and sensation of film on gums (coefficient = 0.625, 95% CI = 0.148–1.103; $p = 0.012$). The association of taste changes ($p = 0.084$) and dry mouth ($p = 0.087$) with depression were non-significant. Note that, although four BMS patients were taking tricyclic antidepressants, controlling for tricyclic antidepressant use as an additional covariate did not change the relation between dry mouth and depressive symptoms ($p = 0.089$).

On linear regression with CIS-R anxiety symptom scores as outcome, again with adjustment for age, sex and BMS diagnosis, taste change (coefficient = 0.269, 95% CI = 0.077–0.461; $p = 0.007$), bad breath (coefficient = 0.273, 95% CI = 0.065–0.482; $p = 0.012$) and fear of serious illness (coefficient = 0.242, 95% CI = 0.036–0.448; $p = 0.023$) had significant associations. Symptoms for which the association with anxiety were not significant but had *p*-values in the range $0.05 < p < 0.075$ were unpleasant taste ($p = 0.053$), burning in the mouth ($p = 0.054$), metallic or acidic taste ($p = 0.066$) and film on teeth or gums ($p = 0.075$).

Addition of a further variable to the model representing use of psychotropic drugs for the relationship of dry mouth and psychiatric morbidity had no impact on the above associations. There was no significant relation between dry mouth and anxiety score, either before or after adjustment for psychotropic drug use. Addition of smoking did not substantially influence the models and, therefore, the above models have been presented without the addition of the smoking variable.

Similar results were produced when analyses were restricted to the 30 participants with BMS diagnoses.

Discussion

Previous studies have reported an association between BMS and psychiatric symptoms or diagnoses.[4,10] This exploratory analysis suggests that certain symptoms, in the context of BMS, may be specifically associated with depression or anxiety disorders. Oral symptoms which are associated with the anxiety measure (predominantly reflecting generalized anxiety symptoms) included burning in the mouth and fear of serious illness, which were two of the three symptoms most consistently and strongly reported in participants with BMS compared with those having other diagnoses. Taste change was the symptom most strongly associated with anxiety symptoms. There is some evidence that taste thresholds change according to circadian rhythm, this fluctuation in taste perception is mediated by cortisol.[17,18] High levels of salivary cortisol have been described in BMS patients.[19] It could be hypothesized that increases in salivary cortisol, a frequent occurrence in anxiety disorders,[20] affect BMS patients more severely. Biopsy studies have also shown axonal degeneration in local nerve fibres.[4] If their gustatory papillae are already damaged, the effect of cortisol may produce non-specific taste changes (increased sensitivity for taste).

Alterations of the hypothalamic pituitary axis, leading to abnormal levels of cortisol, have also been reported in depression. Symptoms associated with depression in this study included bitter or acidic taste. Studies in healthy volunteers have associated noradrenaline and serotonin with changes in the taste threshold; both neurotransmitters are implicated in anxiety and depressive disorders and could be mediating symptoms related to taste.[21]

Since the pathology of BMS is restricted to the oral mucosa it is likely that the deleterious effect of cortisol is palliated to a certain extent by the local excretion of neuroactive steroids by epithelial cells. Neurosteroids are derivatives of gonadal sex hormones. During the menopause these hormones would drop, affecting the local production of these protective substances and leaving the mucosae exposed to the action of corticoids.[22] Cells of the oral mucosa can produce corticoids, but are not able to catabolize these compounds and would be particularly vulnerable to their effects.[23]

What are the clinical ramifications of this study? Dentists should consider questioning patients with BMS about their specific symptoms, as the presence of certain symptoms such as bad breath, taste change and fear of serious illness (generalized anxiety disorder) or metallic/acidic taste and sense of film on teeth or gums (depression) may act as markers to assist in identifying psychiatric diagnoses, a key step in matching the patient to the most appropriate treatment for co-morbid disorders. Although serotonergic antidepressants such as selective serotonin re-uptake inhibitors (SSRIs, e.g. sertraline and citalopram) and serotonin-noradrenaline re-uptake inhibitors (SNRIs, e.g. venlafaxine) are effective in both depression and generalized anxiety disorder, many other antidepressants or anxiolytics do not have strong evidence of efficacy across both disorders. Pregabalin has been used successfully for anxiety in a dental setting [24] and is considered by the British Association of Psychopharmacology Guidelines [25] as an alternative first line treatment for generalized anxiety disorder. Meanwhile, tricyclic antidepressants such as amitriptyline, nortriptyline and imipramine, once a mainstay of treatment for depression and prescribed to four of the patients studied here, carry either limited evidence of effect or lack randomized trial evidence in generalized anxiety disorder entirely.[25] Regarding further care, dentists should consider referral to primary or secondary care in certain circumstances, for example if anxiety or depression symptoms appear severe and/or impair a patient's ability to function normally in their daily activities.

This study requires replication in larger populations. We may have failed to find statistically significant associations between certain putative BMS symptoms and depression or anxiety due to a lack of statistical power. Significance levels were not adjusted for multiple hypothesis testing. While the CIS-R is validated for ascertainment of the outcome measures relating to psychiatric morbidity, our BMS symptom questionnaire based on a review of existing literature was derived for this study and was, therefore, unvalidated. The questionnaire did, however, differentiate symptoms such as burning in the mouth, dry mouth, fear of serious illness and stinging in the mouth as being significantly more common in participants with BMS compared to a comparison group with other dental diagnoses. The failure of metallic/acidic taste, tingling in mouth and teeth clenching to reach significance for this comparison may be due to a type II error reflecting the lack of statistical power. A further limitation was that it was only possible to study depression and anxiety scores as continuous measures, in a larger sample it may be possible to examine the relation of burning mouth symptoms (and symptom clusters identified on factor analysis) with specific disorders. Here, generalized anxiety symptoms of anxiety and worry dominated the sample, with no patient identified as having any other of the anxiety disorders. The present study provides preliminary data on specific oral symptoms which may be used in dentistry as pointers towards the diagnosis of treatable psychiatric disorders in the presence of burning mouth syndrome.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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