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World Workshop on Oral Medicine VII: Burning Mouth Syndrome: A Systematic Review of Disease Definitions and Diagnostic Criteria Utilized in Randomized Clinical Trials

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Running Head: Definitions & Diagnostic Criteria Used in BMS RCTs

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Abstract

Objective: To conduct a systematic review analyzing disease definitions and diagnostic criteria used in randomized controlled trials (RCTs) involving burning mouth syndrome (BMS).

Methods: A systematic search conducted in PubMed, Web of Science, PsycINFO, Cochrane Database/Cochrane Central, and Google Scholar that included RCTs on BMS published between 1994 and 2017 was performed.

Results: Considerable variability in BMS disease definitions and diagnostic criteria used created substantial heterogeneity in the selection of participants and weakened the rigor of

the 36 RCTs identified. The analyzed RCTs routinely under-reported the methods used to rule in or out study participants and the number of individuals excluded from BMS RCTs.

Conclusions: Our findings indicate that a large proportion of participants enrolled in these studies may have had an underlying condition that could have explained their BMS symptoms. Thus, outcomes of therapeutic interventions from the BMS RCTs should be interpreted with caution due to heterogeneous disease definitions and diagnostic criteria. In order to improve the quality of clinical trials, future research should focus on establishing consensus for a single definition of BMS that includes specific inclusion and exclusion criteria that should be used to select study participants for clinical trials.

INTRODUCTION

Burning mouth syndrome (BMS) is characterized by burning pain or discomfort of the tongue, lips or entire oral mucosa without identifiable local or systemic cause (McMillan et al., 2016). Although epidemiological data on BMS are limited (Aravindhan et al., 2014; Zakrzewska JM, 1999), the available literature estimates the prevalence of this disorder is between 0.1% and 3.9% (Kohorst et al., 2015; Bergdahl & Bergdahl, 1999; Netto et al., 2011; Jaaskelainen & Woda, 2017). The majority of cases of BMS occur in females after the age of 50 (Merskey H, 1994; Adamo et al. 2015). BMS symptoms are chronic, have a negative impact on quality of life (Lopez-Jornet et al., 2008; Souza et al., 2011) and affected patients can become high consumers of health care resources (Scala et al., 2003; Hens et al., 2012).

Several definitions of BMS have been published over the past three decades. For example, the International Association for the Study of Pain (IASP) defines BMS (also known as glossodynia, glossopyrosis, oral dysesthesia, or stomatodynia) as “a chronic intraoral burning sensation that has no identifiable cause either local or systemic condition or

disease" (IASP, 2016). The International Headache Society (IHS), in its latest classification of headache disorders (ICHD-3), categorizes BMS under painful neuropathies and defines the condition as "an intraoral burning or dysesthesia sensation, recurring daily for more than two hours per day over more than three months, without clinically evident causative lesions" (IHS, 2018). The World Health Organization publishes a slightly different definition (WHO, 2018) that states BMS is a "chronic orofacial pain with an intraoral burning or dysaesthetic sensation that recurs for more than two hours per day on 50% of the days over more than three months, without evident causative lesions on clinical investigation and examination. It is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) or interference with orofacial functions such as eating, yawning, speaking, etc." With the existence of different disease definitions, investigators who perform randomized controlled trials (RCTs) have the dilemma of which definition to employ.

In addition to disease definition, selection of diagnostic criteria for a given disease is critical when conducting RCTs (Aggarwal et al., 2015). However, development of diagnostic criteria can be complicated due to a poor understanding of the etiology of the disease, varying clinical presentations, and when the diagnosis is made by exclusion. These factors have contributed to the development of different diagnostic criteria for BMS by various organizations and individuals (Bender, 2018, Merskey and Bogduk, 1994; IHS, 2018; IASP, 2013, 2016). For example, the IHS lists the diagnostic criteria as "oral pain fulfilling criteria that recurring daily for >2 hours/day for >3 months and pain has both burning quality and felt superficially in the oral mucosa; oral mucosa is of normal appearance and clinical examination including sensory testing is normal" (IHS, 2018), whereas the IASP (2016) states the "burning sensation is usually daily", with no mention of monthly duration. As a result of these differences, investigators who perform RCTs have little guidance in the selection of appropriate diagnostic criteria.

The lack of consistency across disease definitions and diagnostic (inclusion/exclusion) criteria can result in heterogeneity in case selection. In turn, heterogeneity among RCT participants can contribute to variable effectiveness seen for investigated treatments, as was observed in a recent systematic review of RCTs on BMS (McMillan et al., 2016). This issue is particularly important because clinicians seek accurate interpretation of RCT findings and interventional outcomes. The issue of potential variability in disease definitions and diagnostic criteria in RCTs involving BMS and the subsequent potential variability in the associated outcomes led to the performance of this systematic review.

The objectives of this systematic review were to 1) summarize and assess disease definitions used in BMS RCTs and 2) assess the diagnostic (inclusion and exclusion) criteria used to enroll study participants who were designated to have BMS in RCTs.

MATERIALS AND METHODS

This investigation was conducted as part of the World Workshop on Oral Medicine VII (WWOM VII). The research methods were based on the policies and standards set forth by the Task Force for WWOM IV (Baccaglini et al., 2007) and by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Moher et al., 2010), adapted to the current systematic review.

Protocol Registration

The protocol for this systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO), University of York Center for Review and

Disseminations with identification number CRD42017083266. The registered protocol can be accessed at https://www.crd.york.ac.uk/prospero/#recordDetails.

Search Strategy

A detailed electronic literature search was conducted in the PubMed, Web of Science, PsycINFO, Cochrane Database/Cochrane Central, and Google Scholar in October 2017 using keywords selected based on the study objectives. Details about keywords are provided in **Appendix 1**. A manual search of the literature also was conducted to supplement the electronic search based on references available in selected papers (McMillan et al., 2016, DeSouza et al., 2018).

Literature Search Inclusion Criteria

Inclusion criteria were: RCTs, all age groups, study population of individuals with subjective reporting of burning mouth, affected anatomical locations must include the oral cavity, and at least one subjective and/or objective outcome measure addressing burning mouth was reported in the trial.

Literature Search Exclusion Criteria

Exclusion criteria were: literature published in languages other than English, papers published in non-peer reviewed journals, publications not available in full text, cluster RCTs, review papers, case series, case reports, animal or *in vitro* studies, studies conducted prior to 1994 (i.e., prior to the first acceptable definition of BMS by IASP) (Merskey, 1994). Also excluded were studies that included patients who reported burning exclusively at non-oral

sites, studies concerning other chronic pain conditions and/or widespread pain disorders if BMS participants could not be distinguished from the other conditions.

Studies Selection and Data Extraction Process

Papers identified through the literature search were screened first by reading the titles and abstracts against the inclusion and exclusion criteria. Screening was independently performed by the four reviewers (AA, AF, MC, and RA). Full texts of the papers retained after title and abstract screening were read by the group. The group leader (CM) and two of the consultants, (HF) and (GDK), were consulted if any discrepancies or disagreement occurred during the selection process.

Data from the selected papers were extracted into a table in Excel®. Information regarding the disease definition and diagnostic inclusion and exclusion criteria were extracted. The inclusion criteria focused on symptom quality, location, duration/chronicity, intensity, and modifying factors. Exclusion criteria pertinent to BMS diagnosis were recorded and specifically evaluated for use of: oral mucosal disease, diabetes mellitus (DM), anemia, nutritional deficiencies, oral candidiasis, salivary gland hypofunction/hyposalivation, parafunctional habits, denture use/problems and use of medications that can cause oral burning. This list was generated based on the exclusions suggested by the IASP (2016) and consensus from the group of reviewers and consultants. Methods/tests used to determine exclusion and the number of individuals excluded were recorded. Additional quantitative and qualitative characteristics of each study were collected and are reported in another systematic review on outcome measures. Reviewer calibration was conducted prior to the initiation of data collection by asking all four reviewers (AA, AF, MC and RA) to extract data from specific papers and compare the results. **Figure 1** demonstrates the screening, eligibility and inclusion process.

RESULTS

A total of 3497 papers were identified through electronic (PubMed=1130, Web of Science=1106, Cochrane Central and Cochrane Database=263, PsycINFO=144, Google scholar=851) and manual search=3 (based on reference lists). After removal of duplicates, 2505 papers were available for screening by reading the titles and abstracts for relevance against inclusion and exclusion criteria. Forty papers remained for full text assessment. Having excluded four papers after reading of the full texts, 36 papers remained for qualitative data synthesis (**Figure 1**).

The majority of RCTs were from Europe (n=27); ten from Italy, eight from Spain, two each from Sweden, Denmark and France; one each from Germany, Finland and Croatia. Six RCTs were reported from South America; five from Brazil and one from Argentina. One RCT was reported from the USA. Two RCTs were published by investigators from Japan. **Table 1** provides a summary of the study characteristics.

Definitions

Several different definitions for BMS were used in the 36 RCTs, with international consensus definitions being infrequently cited in the methods section of these publications. The definitions used also varied in their requirements with respect to anatomic site, quality and duration of pain, as well as accompanying features. Of the 36 RCTs, 26 used a consensus definition, or one that resembled a consensus definition, as a tool for case identification (**Table 2**), while ten did not (Bergdahl et al., 1995; Bessho et al., 1998; Femiano et al., 2000; Femiano et al., 2004; Toida et al., 2009; Rodriguez de Rivera Campillo et al., 2010; Lopez-D'alessandro & Escovich, 2011; Heckmann et al., 2012; Treldal et al., 2016; Sugaya et al., 2016).

Criteria for inclusion of subjects in RCT's

Pain quality, intensity, location, and duration (chronicity) are essential pain characteristics used in the assessment of BMS. We reviewed which of these aforementioned characteristics along with modifying factors and triggering events were used as inclusion criteria in the selected RCTs (**Table 3**), and found a median of 3 criteria[1] were used.

One (3%) of the 36 RCTs reported using four inclusion criteria, six (17%) reported use of a single criterion, 12 (33%) reported use of two criteria and 14 (39%) reported three criteria were used (**Table 3**). Quality and chronicity of pain were the most frequently used inclusion criteria (26/36; 72%). Specific symptom location was reported in a minority of RCTs (15/36; 42%); 13 of which enrolled participants with symptoms at any intraoral site and two RCTs limited their participants to only those with symptoms of the tongue. Notably absent was the use of pain intensity as an inclusion criterion (i.e., used in only one RCT). However, pain intensity was reported as an outcome measure in most studies.

Only three RCTs (8%) used "modifying factors" as an inclusion criterion. The following descriptions "pain never worsens, but may be relieved, by eating and drinking" and "does not interfere with sleep" were used to identify this criterion.

An additional pain characteristic that may be important in understanding BMS etiology was "triggering event". Triggering events were reported in four RCTs (11%); these included dental procedure, hot food/drink, stress, car accident and oral infection. Triggering event was not a required diagnostic criterion for any study.

[1] Analysis was based on the use of quality, location, intensity, chronicity and modifying factors in the inclusion criteria.

Criteria for exclusion of subjects from RCT's

Tables 4, 5 and 6 and the paragraphs below summarize the local and systemic conditions excluded in the RCTs. The RCTs reported using on average 4.4 conditions[2] as exclusion criteria. Conditions reviewed included oral mucosal disease, candida infection, salivary gland hypofunction/hyposalivation, DM, anemia, B12 and B9 deficiency and angiotensin converting enzyme (ACE) inhibitors.

Oral mucosal disease

Oral mucosal disease was the most commonly used criterion for exclusion. Thirty-four RCTs (94%) reported that persons with oral mucosal disease were excluded, or only those with clinically normal oral mucosa were included based on a clinical examination. Several RCTs excluded other conditions that could produce oral mucosal pathology or burning discomfort including parafunctional habits (n=5, 14%), problems with dentures (n=7, 19%), atrophy of tongue papilla (n=3, 8%), and benign migratory glossitis (n=3, 8%).

Diabetes mellitus (DM)

The second most common exclusion criterion was DM. Twenty-four RCTs (67%) excluded participants who had DM. Nineteen RCTs (53%) reported using blood glucose to assess the presence of DM; the remaining RCTs did not report how DM was assessed. Six RCTs (17%) indicated that a total of 12 screened individuals were excluded due to an abnormal test result.

[2] The conditions used as exclusion criteria were: oral mucosal disease, oral candidiasis, salivary gland hypofunction/hyposalivation, DM, anemia, B12 and B9 deficiency and ACE inhibitors. Hypothyroidism, autoimmune disorders, trauma and allergies were not considered exclusion criteria in this systematic review because the underlying mechanism for these in BMS is not well documented. Other exclusion criteria not relevant for BMS diagnosis were not reviewed.

Anemia, other hematologic/nutritional deficiencies

Twenty-four (67%) RCTs reported anemia was an exclusion criterion (**Table 6**). Of these, only two RCTs (6%) reported the number of screened individuals excluded based on an abnormal test result. The tests employed for the determination of anemia varied across RCTs. The most commonly employed tests were complete blood count (CBC) (n=19, 53%) and serum iron (n=17, 47%). Transferrin and serum ferritin levels were reported in ten (28%) and eight (22%) RCTs, respectively; of these studies 100% also used a CBC. Vitamin B12 and B9 serum levels were reported in 18 (50%) and 23 (64%) of RCTs, respectively.

Oral candidiasis

Oral candidiasis was the third most commonly excluded condition, with 20 RCTs (55%) listing oral candidiasis as an exclusion criterion (**Table 4**). Only seven (19%) reported the test used for diagnosis; four RCTs used culture and three used cytology. Only two of 36 RCTs (6%) reported the number of screened individuals they excluded (n=18) based on this criterion.

Salivary gland hypofunction/hyposalivation

Salivary gland hypofunction/hyposalivation was the fourth most commonly excluded condition with fourteen RCTs (39%) excluding persons with this condition (**Table 4**). Sialometry was the most commonly employed method to confirm salivary gland hypofunction/hyposalivation, with 13 RCTs (36%) reporting use of this method. Four studies (11%) clearly indicated that a total of 13 individuals were excluded due to salivary gland hypofunction/hyposalivation.

Medications

Four RCTs (11%) excluded individuals who were taking ACE inhibitors. Seven (19%) and six (17%) RCTs excluded those taking antidepressants and anxiolytics respectively (**Table 5**). Only one study (Cavalcanti et al., 2009) listed medications that enrolled participants were concurrently taking.

Autoimmune disorders/thyroid disorders

Autoimmune and thyroid disorders were used as exclusion criteria in six (17%) and seven (19%) RCTs, respectively.

DISCUSSION

BMS has long been studied and many therapeutic modalities have been evaluated. However, to date, consensus on the standard for its management does not exist (de Souza et al., 2018). A recent Cochrane review confirmed the lack of RCTs that provide sufficient guidance to clinicians on effective treatment interventions (McMillan et al., 2016).

Systematic reviews based on RCTs are believed to provide a high level of evidence for managing diseases. However, an important but often overlooked factor in the study design of RCTs is proper implementation of accurate disease definition and diagnostic inclusion and exclusion criteria. Ill-defined or improper use of disease definition and diagnostic criteria can contribute to inaccurate interpretation of therapeutic outcomes (Miller et al., 2018). In as much as the therapeutic approach hinges on proper enrollment of patients with BMS in RCTs, this systematic review sought to assess critically the disease

definition and diagnostic criteria used to allocate participants in RCTs that evaluated interventions for BMS. This is important because BMS is a disorder of exclusion.

Our findings from analysis of 36 RCTs involving therapeutic interventions for BMS showed that i) disease definitions for BMS are varied and variably used, ii) diagnostic inclusion and exclusion criteria are not standardized nor implemented consistently across RCTs, iii) RCTs routinely under-reported the methods used to rule in or out study participants, and iv) the number of individuals excluded from BMS RCTs is under-reported. Together, these issues have potentially compromised case selection and the scientific rigor of existing RCTs on this topic.

Definition

Findings from our analysis demonstrate the presence of several disease definitions for BMS, and this lack of uniformity led to varying case selection in the RCTs. Disease definitions for BMS are published by international associations such as IASP (IASP, 2013, 2016; Merskey, 1994) and IHS (IHS, 2004; IHS, 2013; IHS, 2018). However, different groups of authors with expertise in the field also have published independent definitions (Bergdahl & Anneroth, 1993; Scala et al., 2003; Zakrzewska, 1995; Grinspan et al., 1995).

In this systematic review, nearly 75% of the RCTs used an existing BMS definition to guide case selection (Gremeau-Richard et al., 2004; Sardella et al., 2008; Cavalcanti & da Silveira, 2009; Marino et al., 2010; Lopez-Jornet et al., 2011; Spanemberg et al., 2012; Sardella et al., 1999; Petruzzi et al., 2004; Femiano, 2002; Gremeau-Richard et al., 2010; Spanemberg et al., 2015; Femiano & Scully, 2002), most commonly that by IASP (Gremeau-Richard et al., 2004; Sardella et al., 2008; Cavalcanti & da Silveira, 2009;

Marino et al., 2010; Lopez-Jornet et al., 2011; Spanemberg et al., 2012; Silva et al., 2014; Cano-Carrillo et al., 2014; Palacios-Sanchez et al., 2015; Umezaki et al., 2016; Jorgensen & Pedersen, 2017) or IHS (Carbone et al., 2009; Jurisic Kvesic et al., 2015; Arduino et al., 2016; Valenzuela et al., 2016; Tammiala-Salonen & Forssell, 1999; Lopez-Jornet et al., 2009; Valenzuela & Lopez-Jornet, 2017; Lopez-Jornet et al., 2013). However, the most current BMS definition by IASP and IHS differ (IASP, 2016; IHS, 2018). These different definitions contribute to different selection criteria for enrolling study participants. As a result, it is predictable that heterogeneous study populations are studied. This heterogeneity potentially compromises the validity of interventional outcomes research, makes RCTs less likely to be repeatable, and contributes to confusion amongst clinicians and researchers.

Criteria for inclusion of subjects in RCT's

Inclusion criteria should capture the presenting signs and symptoms of BMS to ensure the persons enrolled truly have the disease being studied. The inclusion criteria should be well established, non-controversial and used consistently across RCTs. Our systematic review demonstrated this is not the case for RCTs involving BMS. The IASP describes seven clinical features of BMS (i.e., pain quality, location, duration, intensity, trigger for disease onset, modifying factors, and associated features).[3] Of these, only pain quality and chronicity were used in the majority of RCTs. Pain location was reported in 42% of RCTs, and median use amongst the RCTs was 3 criteria. This lack of standardization and use is problematic, and contributes to heterogeneity among studies, which limits the capacity of clinicians and scientists to reach consensus about causative factors and effective treatment outcomes.

[3] Although the IASP (2016) lists "associated features" as a BMS clinical feature, this feature was not a requirement for accurate BMS case selection, and thus was not used in the analyses.

The most obvious problem from RCTs that lack standardized inclusion criteria is that it makes it difficult to differentiate true cases of BMS from other conditions. For example, one research group used the following description for inclusion criteria, "symptoms of burning or pain in the oral mucosa of at least 6 months' duration and who presented with a clinically normal mucosa" (Spanemberg et al., 2012; Spanemberg et al., 2015). It is feasible with use of these criteria that a person who had post-herpetic neuralgia (PHN) or other persistent idiopathic oral pain condition could have been enrolled, if only pain quality, location, duration and the absence of a clinical mucosal abnormality are the inclusion criteria used in BMS case selection.

The fact that BMS can involve different oral anatomic sites could make interpretation of BMS RCTs more problematic. Some participants may have burning of the tongue, whereas others may have involvement of the palate, gingiva or labial/buccal mucosa. When the location, number and size of involved sites is under-reported in BMS RCTs (Bergdahl et al., 1995; Tammiala-Salonen & Forssell, 1999; Femiano et al., 2000; Femiano & Scully, 2002; Femiano, 2002, Femiano et al., 2004; Gremeau-Richard et al., 2004; Lopez-Jornet et al., 2013; Palacios-Sanchez et al., 2015; Valenzuela & Lopez-Jornet, 2017), the interpretations of the therapeutic outcomes are compromised by a lack of understanding whether one site responded better than another, or if certain anatomic sites are more difficult to manage.

Another under-reported BMS clinical characteristic in the RCTs studied is 'disease onset' (*i.e.*, did the condition initiate in association with an injurious/stressful event or trigger?). Only four RCTs in this systematic review reported this potentially important historical finding. The importance of a 'trigger' is not yet well understood. However, the presence of a trigger may provide insight into a physiological response to a traumatic insult that is unique compared with those who do not experience an initial triggering event (Jaaskelainen & Woda, 2017; Jaaskelainen, 2018). For example, burning discomfort occurs

in persons who develop PHN, however a majority of persons who develop herpes zoster infection do not experience PHN suggesting unique physiological responses in subsets of the affected patients (Mallick-Searle et al., 2016). Accordingly, triggering events should be more carefully considered in persons suffering from BMS.

Criteria for exclusion of subjects from RCT's

Because the etiology of BMS is unknown, the diagnosis is by exclusion (Feller et al., 2017, IASP, 2016). As such, the contribution of potential local and systemic factors must be carefully considered if true BMS cases are to be included in RCTs (Sardella et al., 2008). The IASP lists examples of conditions that should be excluded (oral mucosal disease, DM, nutritional deficiencies, salivary gland hypofunction/hyposalivation, trauma, oral candidiasis, allergies, hypothyroidism, autoimmune disorders and the use of ACE inhibitors) (IASP, 2016). The RCTs reported using on average 4.4 conditions as exclusion criteria. The most frequently excluded conditions in the RCTs analyzed were oral mucosal disease (94%), DM (67%), anemia (67%), vitamin B9 (64%) and B12 (50%) deficiency, and oral candidiasis (50%), respectively. Salivary gland hypofunction/hyposalivation and use of ACE inhibitors were infrequently utilized criteria. These findings demonstrate the inconsistency in the use of exclusion criteria known to be associated with oral burning complaints.

Of note, salivary gland hypofunction/hyposalivation is an important exclusion criterion that was not consistently used in the RCTs analyzed. Salivary gland hypofunction/hyposalivation was reported as an exclusion criterion in only 39% of studies. This despite the fact that salivary gland hypofunction/hyposalivation is highly associated with burning sensations and comorbidities associated with BMS (Pajukoski et al., 2001; Bergdahl, 2000;Bergdahl & Bergdahl, 2000; Nasri et al., 2007; Soares et al., 2005; Suh et al., 2007;

Toida et al., 2010). Moreover, burning complaints have been shown to develop coincident with the development of salivary gland hypofunction/hyposalivation and xerostomia (Randall et al., 2013) further emphasizing the importance of assessing salivary gland function as an exclusion criterion.

Methods utilized to determine participant eligibility

Critical to understanding the exclusion criteria in RCTs is knowledge of the methods and tests used to determine participant eligibility. Here the methods should be well accepted, standardized and clearly state the tests used, reference ranges, as well as report test findings so readers can understand how the study population was selected and the characteristics of the study population. In the present systematic review, the tests used to exclude conditions (salivary gland hypofunction/hyposalivation, oral candidiasis, DM, anemia) were reported only in 20% to 55% of RCTs. Cytology or culture for candidiasis, blood glucose for DM, CBC for anemia and sialometry for salivary gland hypofunction/hyposalivation were the tests used most frequently to exclude each given condition. However, whether these tests were used appropriately to rule out a given condition is uncertain based on the available information reported.

For example, the diagnosis of DM can be made from two fasting blood glucose measurements or a hemoglobin A1C, yet in our review we found that nearly all studies used a single blood glucose measure and often did not specify whether the blood glucose level was fasting or non-fasting. Similarly, anemia is often defined by the hemoglobin level in a CBC, yet no studies specified which CBC component measure was used to exclude anemia, and RCTs varied in their use of iron, transferrin or ferritin and whether the patient was excluded from the study based on a specific laboratory threshold. With regard to several of the

exclusion criteria, even if an appropriate test had been used, use of different thresholds could have contributed to enrollment of heterogeneous study populations. Clearly, the lack of information on how persons were excluded from RCTs is a major concern uncovered in this systematic review.

Limitations

The RCTs analyzed in this systematic review were limited to articles published only in the English language up through October 2017, and showed a skewed geographic distribution (*i.e.,* a predominance of RCTs conducted in Italy and Brazil) (**Table 1**). Important information regarding the disease definition, diagnostic criteria and methods used to exclude diseases and conditions often was not reported or was unclear to the reviewers. Thus, assessments were based on what the authors chose to disclose clearly in their publications. This at times may have led to an underestimation of the rigor of published RCTs. Also, since there is no consensus on the disease definition and diagnostic criteria to be used to include and exclude patients with BMS, and the list of exclusion criteria formulated by the IASP is not all-inclusive, it is possible that the RCTs failed to exclude potential and important causes of intraoral burning.

CONCLUSIONS

This systematic review demonstrated that over the years there has been substantial heterogeneity in the enrollment and case selection criteria of BMS participants in RCTs. Also, the presence of multiple definitions for BMS and the lack of standardization in diagnostic criteria contribute to lack of rigor in the RCTs to date. Our findings indicate that

a large proportion of participants enrolled in RCTs involving BMS may have had an underlying condition that could have explained their oral burning. This lack of consensus could influence statistic effect size and the findings from these published RCTs; thus results from these RCTs should be interpreted with caution.

Therefore, in order to improve the quality and generalizability of RCTs, future research should focus on establishing a consensus amongst experts for a single disease definition that would include specific diagnostic inclusion and exclusion criteria to be used for enrolling BMS participants into clinical trials. This should be accompanied by deliberate efforts to improve the reporting of diagnostic details, including specific laboratory findings, in RCTs for both the screened and enrolled participant populations. In addition, systematic reviews should consider design factors beyond risk of bias when assessing the quality of the primary studies.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the development of the study protocol, literature search, and the review process. AA and MC drafted the manuscript and the senior author (CM) has supervised the study and edited the manuscript. All authors contributed to the drafting and final version of the manuscript.

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Figure Legends

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline flowchart detailing article selection process.

Table 1: Study characteristics of the RCTs

Author & Year	Country	Sample size			Intervention	
		Total	Case	Control	Test	Control
Bergdahl, Anneroth and Perris, 1995	Sweden	30	15	15	Cognitive therapy	Placebo
Bessho et al., 1998	Japan	200	100	100	Kampo medicine	Diazepam + vitamin B complex
Sardella et al., 1999	Italy	30	10	20*	G1: Benzydamine hydrochloride/topical	G2: Placebo rinse/ topical, G3: no treatment
Tammiala-Salonen and Forssell, 1999	Finland	37	18	19	Trazodone	Placebo
Femiano et al., 2000	Italy	42	21	21	Alpha lipoic acid	Placebo
Femiano and Scully, 2002	Italy	60	30	30	Alpha lipoic acid	Placebo
Femiano, 2002	Italy	80	60***	20	Alpha lipoic acid	Placebo
Femiano, Gombos and Scully, 2004	Italy	192	144***	48	G1: Cognitive psychotherapy; G2: 600 mg/day Alpha lipoic acid; Group C: combination of cognitive psychotherapy & Alpha lipoic acid	Placebo
Grémeau-Richard et al., 2004	France	48	24	24	Clonazepam/topical	Placebo/topical

Petruzzi et al., 2004	Italy	50	25	25	Capsaicin	Placebo
Sardella et al., 2008	Italy	43	21	22	Hypericum perforatum extract	Placebo
Carbone et al., 2009	Italy	66	44**	22	G1: Alpha lipoic acid + vitamins; G2: Alpha lipoic acid	Placebo
Cavalcanti and da Silveira, 2009	Brazil	38	38†	38†	Alpha lipoic acid	Placebo
López-Jornet,Camacho-Alonso, Leon-Espinosa, 2009	Spain	39	23	16	Alpha lipoic acid	Placebo
Toida et al., 2009	Japan	71	36	35	Lafutidine	H2 receptors antagonist (famotidine, cimetidine, nizatidine, ranitidine)
Grémeau-Richard et al., 2010	France	40	20	20	G1: Alpha lipoic acid Vitamins; G2: Alpha lipoic acid	Placebo
Marino et al., 2010	Italy	56	42***	14	G1: capsaicin/topical; G2: Alpha lipoic acid; G3: lysozyme-lactoperoxidase/topical	Placebo (boric acid solution)/ topical
Rodríguez de Rivera-Campillo, 2010	Spain	66	33	33	Clonazepam/topical	Placebo/topical
López-Dalessandro and Escovich, 2011	Argentina	120	60	60	G1: Alpha lipoic acid 600 mg a day; G2: Gabapentin 300 mg a day; G3: combination of both	Placebo (starch & cellulose)
López-Jornet, Camacho-Alonso, Andujar-Mateos, 2011	Spain	50	25	25	Instructions to prevent tongue rubbing on teeth + tongue protector + habit-modifying reminders	Instructions to prevent tongue rubbing against teeth/denture

Heckmann et al., 2012	Germany	20	10	10	Clonazepam	Placebo
Silvestre et al., 2012	Sweden	30	30†	30†	Capsaicin/topical	Placebo/topical
Spanemberg, et al., 2012	Brazil	72	38	34	Herbal Catuama	Placebo
López-Jornet, Camacho-Alonso, Molino-Pagan, 2013	Spain	75	50**	25	G1: tongue protector; G2: tongue protector + aloe vera)/topical	Tongue protector & placebo rinse/ topical
Cano-Carrillo, Pons-Fuster & López- Jornet, 2014	Spain	60	30	30	Virgin olive oil with lycopene 300 ppm spray/PO & topical	Placebo
Silva et al., 2014	Brazil	38	19	19	10% urea /topical	Placebo
Jurisic Kvesic et al., 2015	Croatia	42	20	22	Acupuncture	Clonazepam
Palacios-Sánchez et al., 2015	Spain	54	25	29	Alpha lipoic acid	Placebo
Spanemberg et al., 2015	Brazil	78	59***	19	G1: Infrared laser once/week, G2: infrared laser 3 times/week; G3: red laser 3 times/week	Placebo (sham laser)
Arduino et al., 2016	Italy	33	18	15	Low Level Laser/topical	clonazepam/topical
Sugaya et al., 2016	Brazil	30	15	15	Low level laser	Placebo (sham laser)
Treldal et al., 2016	Denmark	18	9	9	Bupivacaine lozenges/ topical	Placebo
Umezaki et al., 2016	United States of America	26	14	12	Repetitive transcranial magnetic stimulation	Placebo
Valenzuela, Pons-Fuster	Spain	62	31	31	Chamomile 2%	Placebo

& López-Jornet, 2016						
Jorgensen and Pedersen, 2017	Denmark	44	22	22	Capsaicin	Placebo
Valenzuela and López-Jornet, 2017	Spain	44	32**	12	G1: low level laser; G2: low level infrared laser/topical	Placebo (sham laser)

G: Group; PO: per oral.

*10 in each placebo and no treatment, **Two groups, ***Three groups, † Cross over design

Table 2: Definitions used in the RCTs

Definition (Burning Mouth Syndrome (BMS), glossodynia, burning tongue, oral dysesthesia)			Studies that reported in the methods section use of a case definition resembling the definition listed in adjacent column
Consensus Definitions	IASP, 1994	Burning pain in the tongue or other oral mucous membrane.	**2 studies** (Silva et al., 2014, Jorgensen & Pedersen, 2017)
	IHS, 2004	Continuous symptoms of oral burning or pain on a daily or almost daily basis, during all or part of the day for more than 6 months	**8 studies** (Tammiala-Salonen & Forssell, 1999*, López-Jornet et al., 2009, Marino et al., 2010, López-Jornet et al., 2011, Cano-Carrillo et al., 2014, Spanemberg et al., 2012, Jurisic Kvesic et al., 2015, Valenzuela et al., 2016)
	IHS, 2013	Continuous symptoms of oral burning or pain on a daily or almost daily basis during all or part of the day for more than 6 months and the absence of local or systemic factors that could produce the same symptoms	**3 studies** (Lopez-Jornet et al., 2013, Arduino et al., 2016, Valenzuela and López-Jornet, 2017)
Other definitions		- Daily bilateral oral burning (or pain-like sensation) and pain that is experienced deep within the oral mucosa, unremitting for at least 4-6 months, continuous throughout all or almost all day, seldom interferes with sleep, and never worsens, but may be relieved, by eating and drinking - All forms of burning sensation in the mouth, including complaints described as stinging sensation or pain, in association with an oral mucosa that appears clinically normal in the absence of local or systemic diseases or alterations - Burning sensation of the tongue or other oral tissues in the absence of local lesions - Continuous oral burning pain for more than 2 or 4 months with no clinical signs that could justify the syndrome - Continuous symptoms of pain more than 4 months continuous throughout all or part of the day with no paroxysms - Symptoms of burning or pain/discomfort in the oral mucosa for at least 6 months and who presented a clinically normal mucosa - Constant burning discomfort in the tongue, lower lip or hard palate, for more than two months, with no relevant drug or medical history without clinical mucosal lesions or alterations in laboratory parameters	**13 studies** (Sardella et al., 1999, Femiano, 2002, Femiano & Scully, 2002, Gremeau-Richard et al., 2004, Petruzzi et al., 2004, Sardella et al., 2008, Carbone et al., 2009, Cavalcanti and da Silveira, 2009, Gremeau-Richard et al., 2010, Silvestre et al., 2012, Palacios-Sanchez et al., 2015, Spanemberg et al., 2015, Umezaki et al., 2016)

* Used a definition consistent with the IHS (2004) definition, though the study was performed prior to 2004.

Table 3: Inclusion Criteria Reported in Burning Mouth Syndrome (BMS) RCTs

Author & Year	Clinical features used as part of inclusion criteria						Additional clinical features reported[1]	
	Quality	Location	Intensity	Chronicity	Modifying Factors[2]	Number of Clinical Features used as Inclusion Criteria[3]	Intraoral Location	Trigger for Disease Onset
Bergdahl, Anneroth and Perris, 1995	NS	NS	NS	NS	NS	0	NS	NS
Bessho et al., 1998	Pain*	Oral	NS	NS	NS	2	Tongue	NS
Sardella et al., 1999	Burning, Pain, Stinging	Oral	NS	NS	NS	2	Tongue, Gingiva, Lips and/or Labial mucosa, Palate, BM, FOM	NS
Tammiala-Salonen and Forssell, 1999	Burning, Pain	Oral	≥30 on VAS	≥6 mo	NS	4	NS	NS
Femiano et al., 2000	NS	NS	NS	NS	NS	0	NS	NS
Femiano and Scully, 2002	Burning	Oral	NS	≥2 mo	NS	3	NS	NS
Femiano, 2002	Burning	Oral	NS	≥2 mo	NS	3	NS	NS
Femiano, Gombos and Scully, 2004	NS	Oral	NS	NS	NS	1	NS	NS
Grémeau-Richard et al., 2004	Pain	Oral	NS	≥4 mo	NS	3	NS	NS
Petruzzi et al., 2004	Burning	Oral	NS	NS	NS	2	NS	NS
Sardella et al., 2008	Burning	Oral	NS	≥6 mo	NS	3	Tongue, Gingiva, Lips and/or Labial Mucosa, Palate, BM, FOM	NS

Carbone et al., 2009	Pain	Oral	NS	≥4 mo	NS	3	NS	NS
Cavalcanti and da Silveira, 2009	Burning, Pain	Oral	NS	≥6 mo	NS	3	Tongue, Lips and/or Labial Mucosa	NS
López-Jornet,Camacho-Alonso, Leon-Espinosa, 2009	Burning, Pain	Oral	NS	≥6 mo	NS	3	NS	NS
Toida et al., 2009	NS	Oral	NS	≥1 mo	NS	2	NS	NS
Grémeau-Richard et al., 2010	Pain	Oral	NS	≥4 mo	NS	3	Tongue	NS
Marino et al., 2010	Burning	Oral	NS	≥4-6 mo	Yes	4	Tongue, Gingiva, Lips and/or Labial Mucosa, Palate,	NS
Rodríguez de Rivera-Campillo, 2010	Burning	Oral	NS	NS	NS	2	Tongue, Gingiva, Lips and/or Labial Mucosa, Palate	Stress, Chewing, Hot Food/Drink
López-Dalessandro and Escovich, 2011	NS	NS	NS	≥3 mo	NS	1	NS	NS
López-Jornet, Camacho-Alonso, Andujar-Mateos, 2011	Burning, Pain	Oral	NS	≥6 mo	NS	3	NS	NS
Heckmann et al., 2012	NS	NS	NS	NS	NS	0	NS	NS
Silvestre et al., 2012	NS	NS	NS	≥6 mo	NS	1	NS	NS
Spanemberg, et al., 2012	Burning, Pain	Oral	NS	≥6 mo	NS	3	Tongue, Lips and/or Labial Mucosa, Palate	NS

López-Jornet, Camacho-Alonso, Molino-Pagan, 2013	Burning, Pain	Oral	NS	≥6 mo	NS	3	NS	NS
Cano-Carrillo, Pons-Fuster & López-Jornet, 2014	Burning, Pain	Oral	NS	≥6 mo	NS	3	Tongue	NS
Silva et al., 2014	NS	Oral	NS	NS	Yes	2	NS	Stress, Dental Procedure, Coffee, Medications
Kvesic et al., 2015	Burning	Oral	NS	≥6 mo	NS	3	NS	NS
Palacios-Sánchez et al., 2015	Burning	Oral	NS	≥4 mo	NS	3	NS	Stress, Dental Procedure
Spanemberg et al., 2015	Burning, Pain	Oral	NS	≥6 mo	NS	3	Tongue, Lips and/or Labial mucosa, Palate	NS
Arduino et al., 2016	Burning	Oral	NS	≥6 mo	NS	3	NS	NS
Sugaya et al., 2016	NS	NS	NS	NS	NS	0	Tongue, Gingiva, Lips and/or Labial Mucosa, BM, Mandibular Ridge	NS
Treldal et al., 2016	NS	Oral	NS	NR	NS	1	Tongue, Gingiva, Lips and/or Labial Mucosa, Palate, BM	NS
Umezaki et al., 2016	Burning	Oral	NS	≥4-6 mo	Yes	4	Gingiva, Lips and/or Labial Mucosa, Palate,	Dental Treatment, Spontaneous

Valenzuela, Pons-Fuster & López-Jornet, 2016	Burning, Pain	Oral	NS	≥6 mo	NS	3	Tongue, Gingiva, Lips and/or Labial Mucosa, Palate, BM, FOM, Oropharynx	NS
Jorgensen and Pedersen, 2017	Burning, Pain, Stinging	Oral	NS	≥6 mo	NS	3	Tongue, Lips and/or Labial mucosa, Palate, Pharynx, Buccal Mucosa	NS
Valenzuela, López-Jornet, 2017	Burning, Pain	Oral	NS	≥6 mo	NS	3	NS	NS
Studies reporting criteria- n (%)	26 (72%)	30 (83%)	1 (3%)	26 (72%)	3 (8%)	Median: 3	15 (42%)	4 (11%)

BM: Buccal mucosa; FOM: floor of mouth; Mo: month; NS: not specified; VAS: visual analog scale.

[1]: Additional clinical characteristics that were reported for participants enrolled in RCT but not used as part of inclusion criteria.

[2]: "Pain never worsens, but may be relieved, by eating and drinking" and "Does not interfere with sleep"

[3]: Five clinical features of inclusion criteria were counted towards analysis (i.e., quality, location, intensity, chronicity, modifying factors)

*: Glossodynia

Table 4: Exclusion Criteria Reported in Burning Mouth Syndrome (BMS) RCTs – Local Diseases

Author & Year	Oral Mucosal Disease	BMG	Oral Candida Infection	Candida Assessment Methods Used	Salivary Gland Hypofunction/ Hyposalivation	Salivary Gland Hypofunction/ Hyposalivation Assessment Methods Used	PFH	Dentures/ Denture-related problems
Bergdahl, Anneroth and Perris, 1995	Yes	NS	Yes	NS	Unclear***	Yes†	NS	NS
Bessho et al., 1998	Unclear	Unclear*	NS	NS	Yes	NS	Unclear	NS
Sardella et al., 1999	Yes	Yes (1)	Yes	Culture	Yes	Sialometry	Yes (1)	Yes
Tammiala-Salonen and Forssell, 1999	Yes (16)	NS	Yes (14)	NS	Yes (3)	Sialometry	NS	NS
Femiano et al., 2000	Yes	NS	Yes	Culture	Yes	Sialometry	NS	Yes
Femiano and Scully, 2002	Yes	NS	NS	NS	NS	NS	NS	NS
Femiano, 2002	Yes	NS	Yes	Culture	Yes	Sialometry	NS	NS
Femiano, Gombos and Scully, 2004	Yes	NS	NS	NS	Yes	Sialometry	NS	NS
Grémeau-Richard et al., 2004	Yes	NS	Yes††	NS	NS	NS	NS	NS
Petruzzi et al., 2004	Yes	NS	Yes	NS	Yes	Sialometry	NS	NS
Sardella et al., 2008	Yes (1)	NS	Yes	Culture	Yes (3)	Sialometry	Yes(1)	NS

Carbone et al., 2009	Yes	NS	Yes	NS	NS	NS	Yes (1)	NS
Cavalcanti and da Silveira, 2009	Yes (8)	NS	Yes	Cytology	Yes (3)	Sialometry	NS	Yes
López-Jornet,Camacho-Alonso, Leon-Espinosa, 2009	Yes	NS	Yes	NS	NS	NS	NS	Yes
Toida et al., 2009	Yes	NS	Yes	NS	Yes	Sialometry	NS	NS
Grémeau-Richard et al., 2010	Yes	NS	NS	NS	NS	NS	NS	NS
Marino et al., 2010	Yes	Yes	Yes	NS	Yes	NS	Yes (1)	NS
Rodríguez de Rivera-Campillo, 2010	Yes	NS	NS	NS	NS	NS	NS	NS
López-Dalessandro and Escovich, 2011	NS	NS	NS	NS	NS †††	NS	NS	NS
López-Jornet, Camacho-Alonso, Andujar-Mateos, 2011	Yes	Unclear*	Yes	NS	NS	NS	Unclear	Yes
Heckmann et al., 2012	Yes	NS	Yes	NS	NS	NS	NS	NS
Silvestre et al., 2012	Yes	NS	NS	NS	NS	NS	NS	NS
Spanemberg, et al., 2012	Yes	NS	NS	NS	Yes	Sialometry	NS	NS
López-Jornet, Camacho-Alonso, Molino-Pagan, 2013	Yes	Unclear*	Yes	NS	No	NS	Yes (1)	Yes
Cano-Carrillo, Pons-Fuster & López- Jornet, 2014	Yes	Unclear*	Yes	NS	NS	NS	Unclear	Yes
Silva et al., 2014	Yes	NS	NS	NS	Unclear	NS	NS	NS
Kvesic et al., 2015	Yes	NS	NS	NS	No	NS	NS	NS

Palacios-Sánchez et al., 2015	Yes	NS	NS	NS	NS	NS	NS	NS
Spanemberg et al., 2015	Yes	NS	NS	NS	Yes	Sialometry	NS	NS
Arduino et al., 2016	Yes	NS	NS	NS	NS †††	AECG Criteria	NS	NS
Sugaya et al., 2016	Yes	NS	Yes (4)	NS	Yes (4)	Sialometry	NS	NS
Treldal et al., 2016	Yes	NS	Yes	Cytology	Unclear	Sialometry	NS	NS
Umezaki et al., 2016	Yes	NS	NS	NS	NS	NS	NS	NS
Valenzuela, Pons-Fuster & López-Jornet, 2016	Yes	NS	NS	NS	NS †††	NS	NS	NS
Jorgensen and Pedersen, 2017	Yes	Yes	Yes	Cytology	NS	NS	NS	NS
Valenzuela, López-Jornet, 2017	Yes	NS	NS	NS	NS †††	NS	NS	NS
Studies reporting criteria- n [%]	**34 [95%]**	**3 [9%]**	**20 [55%]**	**7 [19%]**	**14 [39%]**	**13 [36%]**	**5 [14%]**	**7 [19%]**

AECG Criteria: American-European consensus group criteria; BMG: benign migratory glossitis; PFH: parafunctional habits; NS: not specified.

( ) Number of cases excluded.

***** Excluded cases with atrophic areas of the tongue.

******Performed oral candidal investigation and if found, was treated, then included in study. No details of test mentioned.

*******Resistant BMS cases were included in the study population.

†Estimated salivary secretion rate, however resistant BMS cases were the study population**,** †† Only when clinically suspected**,** †††Excluded only known Sjögren's syndrome cases.

Table 5: **Exclusion Criteria Reported in Burning Mouth Syndrome (BMS) RCTs – Systemic diseases**

Author & Year	Excluded Systemic Diseases				Excluded Medications		
	DM	DM Assessment Method Used	Autoimmune Disorders	Thyroid Disorders	ACE Inhibitors	Antidepressants	Anxiolytics
Bergdahl, Anneroth and Perris, 1995	NS	NS	Unclear*	Yes	NS	NS	NS
Bessho et al., 1998	NS	NS	NS	NS	NS	NS	NS
Sardella et al., 1999	Yes	BG	NS	NS	NS	NS	NS
Tammiala-Salonen and Forssell, 1999	Yes (1)	BG	NS	NS	NS	NS	NS
Femiano et al., 2000	Yes	BG	NS	NS	NS	NS	NS
Femiano and Scully, 2002	Yes	BG	NS	Yes	NS	NS	NS
Femiano, 2002	Yes	BG	Yes**	NS	NS	NS	NS
Femiano, Gombos and Scully, 2004	Yes	BG	NS	NS	NS	NS	NS
Grémeau-Richard et al., 2004	Yes	NS	NS	NS	NS	Yes	Yes
Petruzzi et al., 2004	NS	NS	NS	NS	NS	NS	NS
Sardella et al., 2008	Yes (2)	BG	NS	NS	No	Yes	NS
Carbone et al., 2009	Yes	BG	NS	NS	Yes	Yes	Yes
Cavalcanti and da Silveira, 2009	Yes (2)	BG	NS	NS	Yes	No	No

López-Jornet,Camacho-Alonso, Leon-Espinosa, 2009	Yes	BG	NS	NS	No	NS	NS
Toida et al., 2009	NS	NS	NS	NS	No	NS	NS
Grémeau-Richard et al., 2010	Yes	NS	NS	NS	No	NS	NS
Marino et al., 2010	Yes	NS	NS	NS	No	NS	NS
Rodríguez de Rivera-Campillo, 2010	NS	NS	NS	NS	No	NS	NS
López-Dalessandro and Escovich, 2011	NS	NS	SS	NS	No	NS	Yes
López-Jornet, Camacho-Alonso, Andujar-Mateos, 2011	Yes	BG	NS	NS	No	Yes	Yes
Heckmann et al., 2012	Yes (1)	NS	NS	NS	No	NS	Yes
Silvestre et al., 2012	NS	NS	NS	NS	No	NS	NS
Spanemberg, et al., 2012	Yes	BG	NS	NS	No	Yes	NS
López-Jornet, Camacho-Alonso, Molino-Pagan, 2013	Yes	BG	NS	Yes	Yes	Yes	NS
Cano-Carrillo, Pons-Fuster & López-Jornet, 2014	Yes	BG	NS	Yes	Yes	Yes	Yes
Silva et al., 2014	NS	NS	NS	NS	No	NS	NS
Kvesic et al., 2015	NS	NS	NS	NS	No	NS	No
Palacios-Sánchez et al., 2015	NS	NS	NS	NS	No	NS	NS
Spanemberg et al., 2015	Yes	BG	NS	NS	No	NS	NS

Arduino et al., 2016	Yes (4)	BG	SS	NS	No	Yes	NS
Sugaya et al., 2016	Yes (2)	BG	NS	NS	NS	NS	NS
Treldal et al., 2016	Yes	BG	NS	Yes	No	NS	NS
Umezaki et al., 2016	NS	NS	Yes	NS	No	NS	NS
Valenzuela, Pons-Fuster & López-Jornet, 2016	Yes†	NS	SS	Yes	No	No	No
Jorgensen and Pedersen, 2017	NS	BG	NS	NS	No	NS	NS
Valenzuela, López-Jornet, 2017	Yes†	NS	SS and *	Yes	No	No	No
Studies reporting criteria- n [%]	**24 [67%]**	**19 [53%]**	**6 [17%]**	**7 [19%]**	**4 [11%]**	**7 [19%]**	**6 [17%]**

ACE: Angiotensin converting enzyme; BG: blood glucose; DM: diabetes mellitus; NS: not specified; SS: S*jö*gren's syndrome

( ) Number of cases excluded

* Rheumatologic diseases (i.e., fibromyalgia and rheumatoid arthritis)

**Anti-nuclear antibody and extractable nuclear antigen positive patients excluded

† Poorly managed diabetes mellitus excluded

Table 6: Exclusion Criteria Reported in Burning Mouth Syndrome (BMS) RCTs – Anaemia and Nutritional Deficiencies

Author & Year	Excluded Anemia	CBC[1]	Serum Iron[1]	Transferrin[1]	Ferritin[1]	Excluded B12 Deficiency	Excluded B9 Folate Deficiency
Bergdahl, Anneroth and Perris, 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bessho et al., 1998	Yes	NS	Yes	NS	Yes	NS	NS
Sardella et al., 1999	Yes	Yes	Yes	Yes	NS	Yes	Yes
Tammiala-Salonen and Forssell, 1999	Yes	Yes	NS	NS	NS	NS	Yes (1)
Femiano et al., 2000	Yes	Yes	NS	NS	Yes	Yes	Yes
Femiano and Scully, 2002	Yes	NS	NS	NS	Yes	NS	Yes
Femiano, 2002	Yes	Yes	NS	NS	Yes	NS	NS
Femiano, Gombos and Scully, 2004	Yes	Yes	NS	NS	Yes	NS	NS
Grémeau-Richard et al., 2004	Yes *	Yes*	Yes*	NS	NS	Yes	Yes
Petruzzi et al., 2004	Yes	Yes	Yes	Yes	Yes	NS	Yes
Sardella et al., 2008	Yes	Yes	Yes	Yes	NS	Yes	Yes
Carbone et al., 2009	Yes	Yes	Yes	Yes	NS	Yes	Yes
Cavalcanti and da Silveira, 2009	Yes	Yes	Yes	Yes	NS	NS	NS

López-Jornet,Camacho-Alonso, Leon-Espinosa, 2009	Yes	Yes	Yes	Yes	NS	NS	NS
Toida et al., 2009	NS	NS	NS	NS	NS	Yes	NS
Grémeau-Richard et al., 2010	Yes	NS	NS	NS	NS	Yes	Yes
Marino et al., 2010	NS	NS	NS	NS	NS	Yes	Yes
Rodríguez de Rivera-Campillo, 2010	NS	NS	NS	NS	NS	Yes	Yes
López-Dalessandro and Escovich, 2011	Yes	NS	NS	NS	NS	NS	NS
López-Jornet, Camacho-Alonso, Andujar-Mateos, 2011	Yes	Yes	Yes	Yes	NS	NS	NS
Heckmann et al., 2012	Yes	NS	Yes	NS	NS	NS	Yes
Silvestre et al., 2012	NS	NS	NS	NS	NS	Yes	Yes
Spanemberg, et al., 2012	Yes	Yes	Yes	NS	NS	Yes	Yes
López-Jornet, Camacho-Alonso, Molino-Pagan, 2013	Yes	Yes	Yes	Yes	NS	NS	NS
Cano-Carrillo, Pons-Fuster & López- Jornet, 2014	Yes	Yes	Yes	Yes	NS	NS	NS
Silva et al., 2014	NS	NS	NS	NS	NS	Yes	Yes

Kvesic et al., 2015	NS	NS	NS	NS	NS	Yes	Yes
Palacios-Sánchez et al., 2015	NS	NS	NS	NS	NS	Yes	Yes
Spanemberg et al., 2015	Yes	Yes	Yes	NS	NS	Yes	Yes
Arduino et al., 2016	Yes	Yes	Yes	NS	NS	Yes	Yes
Sugaya et al., 2016	Yes	Yes	Yes	NS	NS	NS	NS
Treldal et al., 2016	Yes	Yes	Yes	NS	Yes	NS	NS
Umezaki et al., 2016	NS	NS	NS	NS	NS	NS	NS
Valenzuela, Pons-Fuster & López-Jornet, 2016	NS	NS	NS	NS	NS	Yes	Yes
Jorgensen and Pedersen, 2017	NS	NS	NS	NS	NS	NS	Yes
Valenzuela, López-Jornet, 2017	NS	NS	NS	NS	NS	NS	Yes
Studies reporting criteria- n [%]	**24 [67%]**	**20 [55%]**	**18 [50%]**	**10 [28%]**	**8 [22%]**	**18 [50%]**	**23 [64%]**

CBC: complete blood count; NS: not specified

( ) Number of cases excluded

[1]: Excluded if abnormal test result

*Performed only in limited number of cases