**TITLE PAGE**

**Title**

Acute and cumulative benefits of Photobiomodulation for xerostomia: a systematic review and meta-analysis.

**Running title**

Photobiomodulation therapy for xerostomia.

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**ABSTRACT**

The objective was to explore the effectiveness of photobiomodulation therapy for treating patients who suffer xerostomia and/or hyposalivation due to the most prevalent clinical diagnoses. We searched PubMed, Scopus, Web of Science, CINAHL, and Cochrane Library for randomised or clinical controlled trials published until 31 October 2019. Risk of bias assessment and meta-analysis were conducted using the Cochrane tools. A total of 274 records were retrieved and11 met the inclusion criteria. Interventions whose parameters ranged between wavelengths of 790-830nm (infrared), 30-120mW of power, and an energy density below 30J/cm-2 were associated with improvements in xerostomia/hyposalivation. As for the assessment of methodological quality, 10 of the 11 articles included had a high risk of overall bias. Only 3 articles provided sufficient information to conduct a meta-analysis for quality of life, compared with placebo in patients with burning mouth syndrome, showing a standardised mean difference between groups from baseline of -0.90 (-1.48;-0.32). The present review and meta-analysis suggest that photobiomodulation therapy is an effective, non-invasive and safe approach in patients with xerostomia. However, despite the potential, it is not possible to reach a reliable consensus on the parameters to be used, and future studies should be conducted by standardising intervention protocols.

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**INTRODUCTION**

The presentation of dry mouth or xerostomia ranges from mild oral discomfort to significant oral disease that can compromise dietary intake, patient’s health, and quality of life (American Dental Association, 2019). Although medication-induced hyposalivation is the most common cause of dry mouth, arising from polypharmacy in the ageing population (Millsop, Wang, & Fazel, 2017; Ship, Pillemer, & Baum, 2002), head and neck radiation, and Sjögren syndrome are other significant causes, with a prevalence of salivary dysfunction of close to 100% in these patients (Escobar & P. Aitken-Saavedra, 2019). Effective management of this condition is needed to improve quality of life of these patients, and to minimize possible oral and dental complications with associated high cost in public health services (Sasportas et al., 2013).

While these patients may initially present with functional difficulties for swallowing, chewing, speaking or even altered taste, the most significant issues will be dental caries, halitosis, dry buccal mucosa, and burning mouth (Millsop et al., 2017). Unstimulated salivary flow rate (SFR) in patients suffering burning mouth syndrome (BMS) may be decreased (Lee, Hong, Na, & Eun, 2015), suggesting that hyposalivation may play a role in the aetiology of xerostomia in patients with BMS (Teruel & Patel, 2019). This will also in turn compromise oral homeostasis, quality of life, and psychosocial well-being (Millsop et al., 2017), ranging from mild anxiety to major depressive disorder (Cui et al., 2018; Grover & Rhodus, 2016).

Thus, xerostomia and hyposalivation are often challenging conditions in terms of management. Patient education, including basic oral hygiene should be the first step in all cases, followed by avoidance of acidic and spicy food and giving up habits as tobacco or alcohol. In addition, sugar-free chewing gums/candies or toothpastes and mouthwashes tend to stimulate and improve saliva secretion, respectively (Tanasiewicz, Hildebrandt, & Obersztyn, 2016). However, the evidence for these are limited, and they are best considered a basic self-care protocol to achieve certain symptomatic relief (Furness, Worthington, Bryan, Birchenough, & McMillan, 2011). Systemic saliva stimulants such as pilocarpine and cevimeline can also be prescribed. Their effectiveness to minimize xerostomia-derived symptoms is comparable, however, pilocarpine seems to be associated with more side effects (Farag, Holliday, Cimmino, Roomian, & Papas, 2019) as sweating, nausea or stomach upset. Other non-pharmacological means have been studied with varied success including acupuncture (Al Hamad, Lodi, Porter, Fedele, & Mercadante, 2019; Assy & Brand, 2018; Furness, Bryan, McMillan, Birchenough, & Worthington, 2013), as well as such electrophysical agents as electrostimulation (Al Hamad et al., 2019; Furness et al., 2013) or Low Level Laser Therapy (LLLT) (Heiskanen, Zadik, & Elad, 2020; Sousa et al., 2019; Spanemberg, Figueiredo, Cherubini, & Salum, 2016).

LLLT, owing to its photobiological effects (wound healing, anti-inflammatory, antifibrotic and analgesic), has been investigated in both preclinical (Peplow & Baxter, 2012; Peplow, Chung, & Baxter, 2010; Sousa et al., 2019) and clinical studies as isolated or adjuvant therapy (prevention and treatment) for oral disorders such as: oral lichen planus, xerostomia, recurrent aphthous stomatitis, cold sores, BMS, and oral mucositis (Spanemberg et al., 2016). More recently termed Photobiomodulation (PBM), the effects of LLLT/PBM were first reported by Endre Mester (Mester, Szende, & Gärtner, 1968) in Hungary, 50 years ago. The mechanism of action of PBM can be described at three levels: 1) absorption by primary chromophores such as cytochrome c oxidase in mitochondria and calcium ion channels; 2) increase in ATP, nitric oxide, and modulation of calcium levels; and 3) activation of transcription factors (cellular influence) and protein synthesis (M. Hamblin, 2017). PBM has demonstrated potential to reduce xerostomia and hyposalivation (Spanemberg et al., 2016), however there is a lack of synthesis of the evidence to establish whether it is an efficient, safe and cost-effective method (Antunes et al., 2016; Zecha et al., 2016). Challenges in this regard include the lack of consensus on optimal PBM dosage, as well as the variability of findings of published studies (which may in part be based on the former).

A previous systematic review (Furness et al., 2013) evaluated different interventions for the management of dry mouth (regardless of aetiology); however, this review did not retrieve any study focusing on the effectiveness of PBM therapy. More recently, Sousa *et al*. (Sousa et al., 2019) have reviewed the evidence on PBM on dry mouth (to 2018), including studies with multiple aetiology, as well as animal/human designs. Despite its promising findings, this study included a limited database search, no prospective review registration, and did not consider the quality of included studies. This highlights the need for an updated systematic review. Thus, the aim of this systematic review was to explore the effectiveness of PBM therapy for treating patients who suffer xerostomia and/or hyposalivation due to the most prevalent clinical diagnoses.

**MATERIALS AND METHODS**

*Focused question*

A systematic review protocol that defined inclusion criteria, search strategy and outcomes of interest was developed and registered with PROSPERO (CRD42020151145, 26/Feb/2020).Reporting of this systematic review adheres to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). According to PRISMA guidelines, the specific question posed for the review was ‘Is PBM effective in treatment of xerostomia/hyposalivation?’

*Search strategy and eligibility criteria*

Detailed search strategies were developed for each database used in the review: Medline [via PubMed searcher] (**Supplementary Material 1**), Scopus, Web of Science, Cumulative Index for Nursing and Allied Health Literature (CINAHL), and Cochrane Library. The last literature search was conducted on the 31st of October 2019. No restrictions were placed on year of publications, but only published studies in Spanish, English, or Chinese from inception to October 2019 were considered (based upon the research team’s expertise). Studies were included if they met the following criteria: 1) design: randomised controlled trials (RCTs) and clinical controlled trials; 2) population: adults (over 18 years old) with diagnosis of xerostomia and/or hyposalivation of any aetiology; 3) intervention: PBM; 4) control group: placebo, usual care, no intervention or another active intervention. Furthermore, an automatic alert notification for new publications relevant to search term combination was created in all databases from the initial search date. Apart from this, reference lists of retrieved reports were also manually searched for additional references. Two independent researchers (NGC and LL) performed final selection of the studies and appraisal of methodological quality. In case of disagreement, a third external researcher (MLL) was consulted to make the final decision.

*Data extraction and quality assessments*

A data extraction form was developed and tested with the other members of the research team. Once the comments of the group were incorporated, key data extracted from the studies included: authors (year), design (clinical diagnosis), participants, wavelength, spot size, power, mode, energy density, time per point, treatment days, comparison or control, outcome measures, adverse events, measured time points, sites treated, and P-values, and a descriptive summary based on subgroup analysis to update the state of the art in this field. The outcome measures were SFR and/or xerostomia/hyposalivation scores. Further, all articles were checked for reports of adverse effects after PBM. This was used as complementary data to evaluate the safety of this approach. The risk of bias assessment was performed according to the Cochrane Risk of Bias tool: RoB 2 (Sterne et al., 2019). Finally, the quality of the chosen databases was determined by sensitivity/precision analysis (**Supplementary Material 2**).

*Data analysis*

Data from the included studies were pooled for further meta-analysis, but only three out of 11 included studied were assessed due to the substantial heterogeneity in outcomes and groups. Meta-analysis was performed on one outcome: quality of life measured by OralHealth Impact Profile (OHIP). Means and standard deviations for outcome measures (baseline and post-intervention) were extracted from the published data and used to calculate mean difference (MD) and 95% confidence intervals (CIs) in the meta-analysis (change from baseline). Weighted standardised MD between the intervention and control groups was used to quantify the treatment effect. Finally, overall effect size estimator for all studies was calculated. Studies weighting was established according to the degree of precision of each study, using the inverse variance method. All the analyses were carried out with both a fixed-effect and a random-effects model. Heterogeneity between studies was studied statistically by means of the χ2 test and quantified by means of the *I2* index. The following cut-off for reporting heterogeneity was used: less than 25% no heterogeneity, 25-49% low heterogeneity, 50-74% moderate heterogeneity and 75% or greater high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). A study of the publication bias was not carried out using the funnel plot method due to the number of studies included were not enough. The analyses were performed using the OSX version of the statistical program RevMan 5.3 (The Cochrane Collaboration, Oxford, UK).

**RESULTS**

*Study selection*

The search strategy retrieved 274 records, and 54 duplicates were identified and excluded. Two hundred and one records were excluded after screening the titles and abstracts, and the full text of the remaining 19 records was retrieved for detailed assessment. A total of 10 records were excluded for the following reasons: three did not involve relevant clinical diagnoses, two were not RCTs, one was a registry of clinical trial, one was a registry of a clinical trial that was already included, one was a proceedings report, one was written in Russian, and one did not include a relevant outcome measure. Finally, 11 records were included in this systematic review because two additional records were identified, one through hand-searching the reference lists, and the other through automatic alert notifications. Inter-rater agreement in selection of studies was 41.7% (Landis & Koch, 1977). After discussion, the reviewers reached consensus (100%). Details of the literature search and study selection are shown in **Figure 1**.

*Descriptive synthesis*

**Table 1** shows the main characteristics of the interventions carried out in the included studies. A total of 490 subjects participated in the studies included in this review, and the majority was females (n=440). The global mean age was 61.30 years (47.20-69.70) in PBM groups and 59.99 years (46.60-67.67) in control groups. Two studies reported general mean age instead of mean age per group. Despite this, their values were similar or greater than our global means mentioned above; 60.20 (Barbosa et al., 2018) and 67.56 years (Sikora et al., 2018). Considering all 11 studies, 297 subjects were allocated to PBM and 193 were considered controls. Control groups varied in the studies, including placebos (sham laser) (Arbabi-Kalati, Bakhshani, & Rasti, 2015; Bardellini, Amadori, Conti, & Majorana, 2019; Fidelix et al., 2018; Saleh, Figueiredo, Cherubini, Braga-Filho, & Salum, 2014; Sikora et al., 2018; Spanemberg, López López, de Figueiredo, Cherubini, & Salum, 2015; Sugaya et al., 2016; Valenzuela & Lopez-Jornet, 2017) and active treatment (e.g., alpha-lipoic acid, topical clonazepam, and PBM therapy) (Arduino et al., 2016; Barbosa et al., 2018; Brzak et al., 2018). The sample size of the included studies ranged from 20 to 85 subjects. The most frequent diagnosis was BMS (Arbabi-Kalati et al., 2015; Arduino et al., 2016; Barbosa et al., 2018; Bardellini et al., 2019; Sikora et al., 2018; Spanemberg et al., 2015; Sugaya et al., 2016; Valenzuela & Lopez-Jornet, 2017) but effectiveness of PBM for Sjögren syndrome and xerostomia-induced radiotherapy were also evaluated (Fidelix et al., 2018; Saleh et al., 2014). Aetiology of xerostomia/hyposalivation was not described in detail in Brzak *et al*. (Brzak et al., 2018) so has been marked as unknown.

Regarding parameters, there was heterogenicity in terms of wavelength, spot size, power and fluence (J/cm-2) in the included studies (**Table 1**). Some studies did not report spot size used (Brzak et al., 2018; Sikora et al., 2018), energy density (Bardellini et al., 2019), or time per point (Bardellini et al., 2019; Sikora et al., 2018). A few laser parameters that were not reported, were calculated from other reported data (Arbabi-Kalati et al., 2015; Barbosa et al., 2018). Regarding mode of operation, continuous wave was most commonly used (Arduino et al., 2016; Barbosa et al., 2018; Fidelix et al., 2018; Saleh et al., 2014; Spanemberg et al., 2015; Valenzuela & Lopez-Jornet, 2017); one study failed to report it (Arbabi-Kalati et al., 2015).The number of sessions was 4 (Arbabi-Kalati et al., 2015; Barbosa et al., 2018; Sugaya et al., 2016; Valenzuela & Lopez-Jornet, 2017), 9 (Spanemberg et al., 2015), 10 (Arduino et al., 2016; Bardellini et al., 2019; Brzak et al., 2018; Sikora et al., 2018; Spanemberg et al., 2015) and 12 sessions (Fidelix et al., 2018; Saleh et al., 2014). Two sessions per week was the most used frequency of treatment in five out of 11 studies (Arbabi-Kalati et al., 2015; Arduino et al., 2016; Fidelix et al., 2018; Saleh et al., 2014; Sugaya et al., 2016); follow-up ranged from 7 days to 12 weeks after treatment. Different instruments were used to measure outcomes: OHIP (Arbabi-Kalati et al., 2015; Arduino et al., 2016; Bardellini et al., 2019; Saleh et al., 2014; Sikora et al., 2018; Spanemberg et al., 2015; Valenzuela & Lopez-Jornet, 2017)*,* unstimulated and/or stimulated SFR (Barbosa et al., 2018; Brzak et al., 2018; Fidelix et al., 2018; Saleh et al., 2014), xerostomia questionnaires (Fidelix et al., 2018; Valenzuela & Lopez-Jornet, 2017) and visual analogue scale (VAS) symptoms (Saleh et al., 2014; Sugaya et al., 2016).

*Adverse events*

Two RCTs (Arduino et al., 2016; Barbosa et al., 2018) reported adverse effects of (drug based) treatments in control groups, including dizziness, fever, headache and lack of appetite and nausea. There were no PBM-related adverse effects reported.

*Qualitative analysis*

In the subgroup analyses of xerostomia, hyposalivation and quality of life were some differences. Only Sugaya *et al*. (Sugaya et al., 2016) showed that PBM therapy (790 nm) applied in different burning sites reduced more symptoms of xerostomia than placebo in patients with BMS. Similar favourable results for infrared were found on SFR in patients suffering hyposalivation: Brzak *et al*. (Brzak et al., 2018) reported that 830-PBM therapy (830nm) was better than a 685-PBM (685nm) at the same energy density. Finally, quality of life measured by different OHIP versions showed the largest numbers of studies with positive results: four out of seven evaluated OHIP versions found significant improvements in PBM groups (630-970nm) compared with control groups (Arbabi-Kalati et al., 2015; Bardellini et al., 2019; Spanemberg et al., 2015; Valenzuela & Lopez-Jornet, 2017) in patients with BMS. All these clinically relevant improvements refer to acute effects (immediately after treatment); only two studies also assessed cumulative effects (follow-up) finding that improvements were maintained, in particular 4 weeks after PBM for quality of life (Bardellini et al., 2019) and 3 months for xerostomia (Sugaya et al., 2016). The rest of the studies either did not find effects were maintained (Brzak et al., 2018; Spanemberg et al., 2015) or did not report it (Arbabi-Kalati et al., 2015; Valenzuela & Lopez-Jornet, 2017).

*Risk of bias in the included RCTs*

Results of the methodological quality assessment of the 11 included RCTs are shown in **Supplementary Material 3**. The major methodological quality issue was deviations from intended interventions (54.5%), with ‘high risk’ also in overall bias for a total of 90.9% (10/11 studies). In contrast, ‘low risk’ percentages were reported for missing outcome data in 72.7% of the studies, and for measurement of the outcome in 54.5%.

**Supplementary Material 4** shows an assessment summary for each study. Most of the studies included in this systematic review failed (partial or totally) to perform and/or report an appropriate randomisation sequence with correct generation and allocation concealment (63.6%, 7/11). Similarly, all the included studies presented problems or a ‘high risk’ of bias in the selection of the reported results, as they present results evaluated in multiple ways. In addition, the sample size of the included studies was generally ‘low’, with the largest study including 85 subjects. Therefore, none of studies achieved a ‘low’ overall risk of bias; the study by Fidelix *et al*. (Fidelix et al., 2018) demonstrated the least bias (some concerns).

*Meta-analysis*

From a total of 11 retrieved studies, only three (Arbabi-Kalati et al., 2015; Bardellini et al., 2019; Sikora et al., 2018) provided sufficient information to be included in the quantitative meta-analysis; for others, a qualitative summary was presented (as above). For OHIP, the analysis included a joint sample of 149 participants; all these studies compared PBM to placebo in patients with BMS. Statistical analysis showed a standardised MD between groups from baseline of -0.90 (-1.48; -0.32), statistically significant. Given the observed moderate heterogeneity (*I2*=59%, p=0.09) (Higgins et al., 2003), results of the random effects model are presented (**Figure 2**).

**DISCUSSION**

The main finding of this review was that PBM therapy has shown promising effects in the management of xerostomia/hyposalivation induced by multiple aetiology. These findings were regardless of comparison (PBM, control or both), and in favour of PBM therapy in more than a half of studies analysed.

PBM interventions whose parameters ranged between wavelengths of 790-830nm (infrared), 30-120mW of power, and an energy density below 30J/cm-2 were associated with improvements in xerostomia/hyposalivation (compared with placebo).

Energy density (fluence) has been proposed as a key parameter in determining the effects in salivary glands (Zecha et al., 2016), with 30 J/cm-2 being regarded as an upper limit. In this review, 3 studies reporting results in favour of PBM intervention met this condition (Arbabi-Kalati et al., 2015; Brzak et al., 2018; Sugaya et al., 2016). The remaining studies used energy densities above 30 J/cm-2, but with less consistent benefits (with or without significant results). Although this makes it difficult to identify a definitive dosage recommendation, it is important to note that regardless of the dosage used, there were no adverse effects reported in the reviewed studies.

With regards to wavelength, the optimal window for tissue penetration is recognised as between visible red and near-infrared wavelengths (M. Hamblin, 2017), typically from 600 to 1000nm. While all of the studies included here met this window (Lončar, Mravak Stipetić, Baričević, & Risović, 2011), a narrower spectrum (790-830nm) might be more appropriate for treatment of this condition according to our analysis (Brzak et al., 2018; Spanemberg et al., 2015; Sugaya et al., 2016; Valenzuela & Lopez-Jornet, 2017); indeed, water and oxyhaemoglobin are the main chromophores in oral soft tissue (M. R. Hamblin & Demidova, 2006).

PBM therapy is usually based on application of PBM devices lower than 500mW (Class IIIb); this typically reflects statutory and regulatory limits, based upon risk of injury. While most studies used power outputs within this limit, two authors (Bardellini et al., 2019; Valenzuela & Lopez-Jornet, 2017) reported much higher power values (3200 and 1000mW, respectively); however none of them reported adverse effects.

Regarding sites treated, there was variability in the number of treatment points reported, or these were described generically (e.g. painful or burning areas) without anatomical description.

Finally, continuous mode was reported being used in all studies; there was no assessment of the potential benefits of other forms of delivery (i.e. pulsing). There is little knowledge about the clinical implications of specific pulse frequencies in PBM (Tuner, J, Hode, L, 2002). However it is known that, on the one hand, specific pulsing frequencies may have a positive effect on macrophage action (Rajaratnam, Bolton, & Dyson, 1994) and, on the other, chronic conditions are recommended to be treated with continuous mode (Baxter, 2003).

Despite our attempts to establish a consensus in terms of the range of parameters more useful, inconsistent reporting in all studies limits this. This is despite a published framework to improve the reporting of PBM parameters (Zecha et al., 2016). Despite this, it is important to stress that there were no reports of adverse effects related to PBM therapy, demonstrating once again that it is safe and well-tolerated approach. Furthermore, it is important to indicate that PBM therapy does not have only acute effects, but also seems to have cumulative effects on xerostomia and quality of life up to 4- and 12-weeks after completion of PBM therapy.

The majority of the RCTs retrieved by this review deal with xerostomia related to BMS. Our search strategy did not identify papers on the impact of PBM in patients with medication-induced hyposalivation, despite its higher prevalence (Millsop et al., 2017; Ship et al., 2002). A study protocol has been published recently to evaluate the effect of PBM in patients with antihypertensive drug-induced xerostomia (Varellis et al., 2020) so that may endorse the need for further studies that deal with this population. Our review also did not retrieve studies on patients who had undergone radiotherapy, despite the recognised glandular changes associated with the irradiation (Avila, Grundmann, Burd, & Limesand, 2009) that involved xerostomia/hyposalivation, both dose-dependent. This might be explained because one of our exclusion criteria was acute complaints, where PBM therapy may have direct exposure or treatment areas close of the tumour site (Elad et al., 2018), as cancers cells could be exposed to laser irradiation (M. R. Hamblin, Nelson, & Strahan, 2018). For this reason, patients undergoing chemoradiotherapy were excluded.

Due to the high clinical diversity among the studies in this review, in terms of clinical diagnoses, participants, comparison and/or outcomes, it was not possible to perform a meta-analysis with all of them; so it was performed only for subjects whose quality of life measured with OHIP, with two groups (PBM vs placebo). In line with the conclusions drawn from the descriptive analysis, results of the meta-analysis appear to support the effectiveness of PBM, at least compared to placebo. However, these results should be interpreted with caution due to the risk of bias in studies, as well as the heterogeneity detected in the meta-analysis. The assessment of bias indicated that none of the three included studies were free of bias in the blinding and randomisation process. The scientific literature suggests that lack of blinding tends to lead to an overestimation of the treatment effect (Savović et al., 2012). Similarly, although only those studies that reported similar data were included in the meta-analysis, moderate statistical heterogeneity was found. The differences in PBM parameters and treatment days may also contribute to this heterogeneity.

To the best of our knowledge, a sensitivity/precision analyses to identify relevant databases has never been documented within this area. Cochrane recorded the highest sensitivity (100%). High sensitivity scores may reduce the chance of missing papers that are relevant. This study highlighted a low-moderate precision in searching five databases on this topic, despite a detailed search formula and the expertise of a specialist librarian. CINAHL had a sensitivity of 20% and precision of 2.32, indicating that was the most ineffective for use within this review. CINAHL is a highly specialized international database, whose main focus is nursing and allied health, with most resources being citation-only; this may explain this finding. Given the extremely small provision of exclusive references (Beckles et al., 2013), and the additional effort required to translate the search strategy across different databases, we might reconsider the appropriateness of the use of CINAHL within future searches about PBM and xerostomia/hyposalivation (Beckles et al., 2013).

To our knowledge, this is the first review study evaluating the effect of PBM on xerostomia and hyposalivation in humans, and with multiple aetiologies. The strengths of this review are reporting according to the PRISMA guidelines; inclusion of risk of bias assessment; meta-analysis; and sensitivity/precision analyses that may inform future search strategies. Limitations in published reports restricted our ability to determine those parameters of the interventions that were effective; a further limitations include meta-analysis comprises only three studies and none of studies achieved a low overall risk of bias assessment.

In summary, this systematic review identified some acute and cumulative benefits of PBM with regard to xerostomia and quality of life. The rest of the studies also found positive results in PBM or control groups (or both) for all outcomes studied, except Sikora *et al*. (Sikora et al., 2018). Despite the potential of PBM interventions, it has not been possible to reach a reliable consensus for all parameters analysed, due to the disparity in the data retrieved. Furthermore, a high proportion of studies targeted only patients with BMS, so future studies should ensure that interventions are tested in other problematic clinical entities. This review adds to the growing evidence supporting PMB interventions to treat xerostomia and hyposalivation as an effective, non-invasive, and safe approach.

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**AUTHOR CONTRIBUTIONS**

N. Galiano-Castillo, S. Tumilty, and G.D. Baxter conceptualized the review and drafted the manuscript. N. Galiano-Castillo, L. Liuand M. Lozano-Lozano set up the search strategy and assessment of quality included in the manuscript. N. Galiano-Castillo, M. Lozano-Lozano and I. Cantarero-Villanueva involved in data extraction and data analysis. L. Liu, S. Tumilty, and G.D. Baxter revised the manuscript critically. All authors read and provided amendment on the draft and confirmed the final manuscript.

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**REFERENCES**

Al Hamad, A., Lodi, G., Porter, S., Fedele, S., & Mercadante, V. (2019, May 1). Interventions for dry mouth and hyposalivation in Sjögren’s syndrome: A systematic review and meta-analysis. *Oral Diseases*. Blackwell Publishing Ltd. https://doi.org/10.1111/odi.12952

American Dental Association. (2019). Xerostomia (Dry Mouth). Retrieved April 21, 2020, from https://www.ada.org/en/member-center/oral-health-topics/xerostomia

Antunes, H. S., Schluckebier, L. F., Herchenhorn, D., Small, I. A., Araújo, C. M. M., Viégas, C. M. P., … Ferreira, C. G. (2016). Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. *Oral Oncology*, *52*, 85–90. https://doi.org/10.1016/j.oraloncology.2015.10.022

Arbabi-Kalati, F., Bakhshani, N.-M., & Rasti, M. (2015). Evaluation of the efficacy of low-level laser in improving the symptoms of burning mouth syndrome. *Journal of Clinical and Experimental Dentistry*, *7*(4), e524-7. https://doi.org/10.4317/jced.52298

Arduino, P. G., Cafaro, A., Garrone, M., Gambino, A., Cabras, M., Romagnoli, E., & Broccoletti, R. (2016). A randomized pilot study to assess the safety and the value of low-level laser therapy versus clonazepam in patients with burning mouth syndrome. *Lasers in Medical Science*, *31*(4), 811–816. https://doi.org/10.1007/s10103-016-1897-8

Assy, Z., & Brand, H. S. (2018). A systematic review of the effects of acupuncture on xerostomia and hyposalivation. *BMC Complementary and Alternative Medicine*, *18*(1), 57. https://doi.org/10.1186/s12906-018-2124-x

Avila, J. L., Grundmann, O., Burd, R., & Limesand, K. H. (2009). Radiation-Induced Salivary Gland Dysfunction Results From p53-Dependent Apoptosis. *International Journal of Radiation Oncology Biology Physics*, *73*(2), 523–529. https://doi.org/10.1016/j.ijrobp.2008.09.036

Barbosa, N. G., Gonzaga, A. K. G., de Sena Fernandes, L. L., da Fonseca, A. G., Queiroz, S. I. M. L., Lemos, T. M. A. M., … de Medeiros, A. M. C. (2018). Evaluation of laser therapy and alpha-lipoic acid for the treatment of burning mouth syndrome: a randomized clinical trial. *Lasers in Medical Science*, *33*(6), 1255–1262. https://doi.org/10.1007/s10103-018-2472-2

Bardellini, E., Amadori, F., Conti, G., & Majorana, A. (2019). Efficacy of the photobiomodulation therapy in the treatment of the burning mouth syndrome. *Medicina Oral Patologia Oral y Cirugia Bucal*, *24*(6), e787–e791. https://doi.org/10.4317/medoral.23143

Baxter, G. D. (2003). Low intensity laser therapy. In eds. Kitchen S, Bazin S (Ed.), *Electrotherapy: Evidence-Based Practice.* London: WB Saunders.

Beckles, Z., Glover, S., Ashe, J., Stockton, S., Boynton, J., Lai, R., & Alderson, P. (2013). Searching CINAHL did not add value to clinical questions posed in NICE guidelines. *Journal of Clinical Epidemiology*, *66*(9), 1051–1057. https://doi.org/10.1016/j.jclinepi.2013.04.009

Brzak, B. L., Cigić, L., Baričević, M., Sabol, I., Mravak-Stipetić, M., & Risović, D. (2018). Different Protocols of Photobiomodulation Therapy of Hyposalivation. *Photomedicine and Laser Surgery*, *36*(2), 78–82. https://doi.org/10.1089/pho.2017.4325

Cui, Y., Xia, L., li, L., Zhao, Q., Chen, S., & Gu, Z. (2018). Anxiety and depression in primary Sjögren’s syndrome: a cross-sectional study. *BMC Psychiatry*, *18*(1), 131. https://doi.org/10.1186/s12888-018-1715-x

Elad, S., Arany, P., Bensadoun, R. J., Epstein, J. B., Barasch, A., & Raber-Durlacher, J. (2018, October 1). Photobiomodulation therapy in the management of oral mucositis: search for the optimal clinical treatment parameters. *Supportive Care in Cancer*. Springer Verlag. https://doi.org/10.1007/s00520-018-4262-6

Escobar, A., & P. Aitken-Saavedra, J. (2019). Xerostomia: An Update of Causes and Treatments. In *Salivary Glands - New Approaches in Diagnostics and Treatment*. IntechOpen. https://doi.org/10.5772/intechopen.72307

Farag, A. M., Holliday, C., Cimmino, J., Roomian, T., & Papas, A. (2019). Comparing the effectiveness and adverse effects of pilocarpine and cevimeline in patients with hyposalivation. *Oral Diseases*, *25*(8), 1937–1944. https://doi.org/10.1111/odi.13192

Fidelix, T., Czapkowski, A., Azjen, S., Andriolo, A., Neto, P. H., & Trevisani, V. (2018). Low-level laser therapy for xerostomia in primary Sjögren’s syndrome: a randomized trial. *Clinical Rheumatology*, *37*(3), 729–736. https://doi.org/10.1007/s10067-017-3898-9

Furness, S., Bryan, G., McMillan, R., Birchenough, S., & Worthington, H. V. (2013). Interventions for the management of dry mouth: non-pharmacological interventions. In S. Furness (Ed.), *Cochrane Database of Systematic Reviews* (p. CD009603). Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.CD009603.pub3

Furness, S., Worthington, H. V, Bryan, G., Birchenough, S., & McMillan, R. (2011). Interventions for the management of dry mouth: topical therapies. *Cochrane Database of Systematic Reviews*, (12). https://doi.org/10.1002/14651858.cd008934.pub2

Grover, S. S., & Rhodus, N. L. (2016). Xerostomia and Depression. *Northwest Dentistry*, *95*(3), 29, 31, 33–35. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27476240

Hamblin, M. (2017). Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS Biophysics*, *4*(3), 337–361. https://doi.org/10.3934/biophy.2017.3.337

Hamblin, M. R., & Demidova, T. N. (2006). Mechanisms of low level light therapy. In *Mechanisms for Low-Light Therapy* (Vol. 6140, p. 614001). SPIE. https://doi.org/10.1117/12.646294

Hamblin, M. R., Nelson, S. T., & Strahan, J. R. (2018, May 1). Photobiomodulation and Cancer: What Is the Truth? *Photomedicine and Laser Surgery*. Photomed Laser Surg. https://doi.org/10.1089/pho.2017.4401

Heiskanen, V., Zadik, Y., & Elad, S. (2020). Photobiomodulation Therapy for Cancer Treatment-Related Salivary Gland Dysfunction: A Systematic Review. *Photobiomodulation, Photomedicine, and Laser Surgery*, photob.2019.4767. https://doi.org/10.1089/photob.2019.4767

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003, September 6). Measuring inconsistency in meta-analyses. *British Medical Journal*. BMJ Publishing Group. https://doi.org/10.1136/bmj.327.7414.557

Landis, J. R., & Koch, G. G. (1977). The Measurement of Observer Agreement for Categorical Data. *Biometrics*, *33*(1), 159. https://doi.org/10.2307/2529310

Lee, Y. C., Hong, I. K., Na, S. Y., & Eun, Y. G. (2015). Evaluation of salivary function in patients with burning mouth syndrome. *Oral Diseases*, *21*(3), 308–313. https://doi.org/10.1111/odi.12270

Lončar, B., Mravak Stipetić, M., Baričević, M., & Risović, D. (2011). The Effect of Low-Level Laser Therapy on Salivary Glands in Patients with Xerostomia. *Photomedicine and Laser Surgery*, *29*(3), 171–175. https://doi.org/10.1089/pho.2010.2792

Mester, E., Szende, B., & Gärtner, P. (1968). [The effect of laser beams on the growth of hair in mice]. *Radiobiologia, Radiotherapia*, *9*(5), 621–626. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5732466

Millsop, J. W., Wang, E. A., & Fazel, N. (2017). Etiology, evaluation, and management of xerostomia. *Clinics in Dermatology*, *35*(5), 468–476. https://doi.org/10.1016/j.clindermatol.2017.06.010

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Peplow, P. V., & Baxter, G. D. (2012). Gene Expression and Release of Growth Factors During Delayed Wound Healing: A Review of Studies in Diabetic Animals and Possible Combined Laser Phototherapy and Growth Factor Treatment to Enhance Healing. *Photomedicine and Laser Surgery*, *30*(11), 617–636. https://doi.org/10.1089/pho.2012.3312

Peplow, P. V., Chung, T.-Y., & Baxter, G. D. (2010). Laser Photobiomodulation of Proliferation of Cells in Culture: A Review of Human and Animal Studies. *Photomedicine and Laser Surgery*, *28*(S1), S-3-S-40. https://doi.org/10.1089/pho.2010.2771

Rajaratnam, S., Bolton, P., & Dyson, M. (1994). Macrophage Responsiveness to Laser Therapy with Varying Pulsing Frequencies. *LASER THERAPY*, *6*(2), 107–112. https://doi.org/10.5978/islsm.94-OR-04

Saleh, J., Figueiredo, M. A. Z., Cherubini, K., Braga-Filho, A., & Salum, F. G. (2014). Effect of Low-Level Laser Therapy on Radiotherapy-Induced Hyposalivation and Xerostomia: A Pilot Study. *Photomedicine and Laser Surgery*, *32*(10), 546–552. https://doi.org/10.1089/pho.2014.3741

Sasportas, L. S., Hosford, D. N., Sodini, M. A., Waters, D. J., Zambricki, E. A., Barral, J. K., … Sirjani, D. (2013). Cost-effectiveness landscape analysis of treatments addressing xerostomia in patients receiving head and neck radiation therapy. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. Mosby Inc. https://doi.org/10.1016/j.oooo.2013.02.017

Savović, J., Jones, H. E., Altman, D. G., Harris, R. J., Jüni, P., Pildal, J., … Sterne, J. A. C. (2012). Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Annals of Internal Medicine*, *157*(6), 429–438. https://doi.org/10.7326/0003-4819-157-6-201209180-00537

Ship, J. A., Pillemer, S. R., & Baum, B. J. (2002, January 1). Xerostomia and the geriatric patient. *Journal of the American Geriatrics Society*. https://doi.org/10.1046/j.1532-5415.2002.50123.x

Sikora, M., Včev, A., Siber, S., Vučićević Boras, V., Rotim, Ž., & Matijević, M. (2018). The Efficacy of Low-Level Laser Therapy in Burning Mouth Syndrome - A Pilot Study. *Acta Clinica Croatica*, *57*(2), 312–315. https://doi.org/10.20471/acc.2018.57.02.12

Sousa, A. S., Silva, J. F., Pavesi, V. C. S., Carvalho, N. A., Ribeiro-Júnior, O., Varellis, M. L. Z., … Deana, A. M. (2019, November 25). Photobiomodulation and salivary glands: a systematic review. *Lasers in Medical Science*. Springer. https://doi.org/10.1007/s10103-019-02914-1

Spanemberg, J. C., Figueiredo, M. A. Z., Cherubini, K., & Salum, F. G. (2016). Low-level Laser Therapy: A Review of Its Applications in the Management of Oral Mucosal Disorders. *Alternative Therapies in Health and Medicine*, *22*(6), 24–31. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27866178

Spanemberg, J. C., López López, J., de Figueiredo, M. A. Z., Cherubini, K., & Salum, F. G. (2015). Efficacy of low-level laser therapy for the treatment of burning mouth syndrome: a randomized, controlled trial. *Journal of Biomedical Optics*, *20*(9), 098001. https://doi.org/10.1117/1.JBO.20.9.098001

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., … Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, *366*, l4898. https://doi.org/10.1136/bmj.l4898

Sugaya, N. N., Silva, É. F. P. da, Kato, I. T., Prates, R., GALLO, C. B. de B., & Pellegrini, V. D. (2016). Low Intensity laser therapy in patients with burning mouth syndrome: a randomized, placebo-controlled study. *Brazilian Oral Research*, *30*(1), e108. https://doi.org/10.1590/1807-3107BOR-2016.vol30.0108

Tanasiewicz, M., Hildebrandt, T., & Obersztyn, I. (2016). Xerostomia of Various Etiologies: A Review of the Literature. *Advances in Clinical and Experimental Medicine*, *25*(1), 199–206. https://doi.org/10.17219/acem/29375

Teruel, A., & Patel, S. (2019). Burning mouth syndrome: A review of etiology, diagnosis, and management. *General Dentistry*. Academy of General Dentistry.

Tuner, J, Hode, L. (2002). *Laser Therapy—Clinical Practice and Scientific Background*. Grangesberg: Prima Books.

Valenzuela, S., & Lopez-Jornet, P. (2017). Effects of low-level laser therapy on burning mouth syndrome. *Journal of Oral Rehabilitation*, *44*(2), 125–132. https://doi.org/10.1111/joor.12463

Varellis, M. L. Z., Gonçalves, M. L. L., Pavesi, V. C. S., Horliana, A. C. R. T., de Fátima Teixeira da Silva, D., Motta, L. J., … Deana, A. M. (2020). Evaluation of photobiomodulation in salivary production of patients with xerostomy induced by anti-hypertensive drugs. *Medicine*, *99*(16), e19583. https://doi.org/10.1097/md.0000000000019583

Zecha, J. A. E. M., Raber-Durlacher, J. E., Nair, R. G., Epstein, J. B., Sonis, S. T., Elad, S., … Bensadoun, R.-J. (2016). Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. *Supportive Care in Cancer*, *24*(6), 2781–2792. https://doi.org/10.1007/s00520-016-3152-z

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| **Authors**  **Table 1** Characteristics of 11 RCTs regarding PBM therapy for xerostomia and hyposalivation.  GREY  **(year)**  **Design**  **(clinical diagnosis)** | **Participants** | **Wave-**  **length**  **(nm)** | **Spot size**  **(cm-2)** | **Power**  **(mW)** | **Mode (distance)** | **Energy density**  **(J/cm-2)** | **Time/point**  **(s)** | **Treatment days**  **(total sessions)** | **Comparison**  **or control** | **Outcome**  **measures** | **Adverse events** | **Measured time points** | **Sites treated** | **P-values** |
| **Arbabi-Kalati et al. (2015)**‡  RCT  BMS | *PBM*  n=10  *Control*  n=10 | 630 | 0.3§ | 30 | Not  specified | 1 | 10 | 2/wk  2wk  (4) | Placebo | **OHIP-14** | No reported | Baseline  After treatment | 10 intraoral points  (2-buccal mucosa bilaterally, 2-tongue, 2-floor of the mouth, 1-soft palate, 1-hard palate) | OHIP-14  ***Between group effects***  *P*=0.01†  (after, *PBM>Control*) |
| **Arduino et al. (2016)**  RCT  BMS | *PBM*  n=18  *Control*  n=15 | 980 | 0.28 | 300 | Continuous  (2 mm) | 10 | 10 | 2/wk  5wk  (10) | Topical clonazepam  therapy | **OHIP-49** | *PBM:* no reported  *Control:* dizziness  fever  headache lack of appetite | Baseline  *Follow-up:*  12 wk after treatment | Burning sites  (up to 0.5 cm beyond borders) | OHIP-49  ***Within group effects***  *P*=0.01†  (12wk*, PBM*)  *P*=0.25  (12wk*, Control*)  ***Between group effects***  *P*=0.193  (12wk) |
| **Barbosa et al.**  **(2018)**  RCT  BMS  SOB | *PBM BMS*  n=10  *ALA BMS*  n=5  *PBM SOB*  n=15  *ALA SOB*  n=14 | 660 | 0.1§ | 30 | Continuous  (contact) | 3 | 10 | 1/wk  4wk  (4) | ALA | **Unstimulated SFR**  (ml/min) | *PBM BMS-SOB:*  No reported  *ALA:*  headache nausea | Baseline  After treatment | Burning sites | SFR  ***Within group effects***  *P*=0.034†  (baseline-after, *PBM BMS*)  *P*=0.414  (baseline-after*, ALA BMS*)  ***Within group effects***  *P*=0.427  (baseline-after, *PBM SOB*)  *P*=0.622  (baseline-after, *ALA SOB*) |
| **Bardellini et al. (2019)**‡  RCT  BMS | *PBM*  n=43  *Control*  n=42 | 660-970 | 1 | 3200  (6400 pulsed at 50%) | Discontinuous | Not specified | Not specified | 1/wk  10wk  (10) | Placebo | **OHIP-14** | No reported | Baseline  After each session  *Follow-up:*  4 wk  after treatment | Painful areas | OHIP-14  ***Between group effects***  *P*<0.05†  (after 7º-10º sessions, *PBM>Control*)  ***Between group effects***  *P*=0.0002†  (after 4wk, *PBM>Control*) |
| **Brzak et al. (2018)**  RCT  Unknown | *685-PBM* n=15  *830-PBM* n=15 | 685  vs.  830 | Not specified | *685-PBM*  30  *830-PBM*  35 | Pulsed 5.2Hz  Manual scanning  (5 mm) | 1.80 | *685-PBM*  300-parotid  120-submandibular  60-sublingual  Total=480  *830-PBM*  257-parotid  103-submandibular  51-sublingual  Total= 411 | Consec.  (10) | N/A | **Unstimulated SFR**  (ml/min) | No reported | Baseline  d1-d10  *Follow-up:*  10+ days  after treatment | 4 extraoral points bilaterally  (1-parotid, 1-submandibular)  2 intraoral points bilaterally (1-sublingual) | SFR  ***Within group effects***  *P*=0.0044†  (baseline-d10, *685-PBM*)  *P*=0.0121†  (baseline-10+, *685-PBM 685*)  *P*=0.0019†  (baseline-d10, *830-PBM*)  *P*=0.0347†  (baseline-10+, *830-PBM*)  ***Between group effects***  *P*<0.01†  (baseline-d10, *830*-*PBM* >*685-PBM*)  *P*>0.05  (baseline-10+) |
| **Fidelix et al. (2018)**  RCT  Primary SS | *PBM*  n=33  *Control*  n=33 | 808 | 0.03 | 100 | Continuous  (contact) | 133 | 40 | 2/wk  6wk  (12) | Placebo | **Xerostomia inventory (XI)**  **Stimulated SFR**  (ml/min) | No reported | Baseline  After treatment | 12 extraoral points bilaterally  (4-parotid and 2-submandibular)  4 intraoral points bilaterally (2-sublingual) | Xerostomia inventory (XI)  ***Within group effects***  *P*=0.003†  (baseline-after, *PBM*)  *P*=0.003†  (baseline-after, *Control*)  ***Between group effects***  *P*=0.301  (baseline-after)  SFR  ***Within group effects***  *P*=0.562  (baseline-after, *PBM*)  *P*=0.562  (baseline-after, *Control*)  ***Between group effects***  *P*=0.643  (baseline-after) |
| **Saleh et al. (2014)**  RCT  HNC RT | *PBM*  n=12  *Control*  n=11 | 830 | 0.028 | 100 | Continuous  (contact) | 71 | 20 | 2/wk  6wk  (12) | Placebo | **VAS xerostomia**  **Stimulated and unstimulated SFR**  (ml/min)  **OHIP-14** | No reported | Baseline  3 wk  6 wk | 10 extraoral points bilaterally  (3-parotid and 2-submandibular)  4 intraoral points bilaterally (2-sublingual) | VAS  ***Within group effects***  *P*<0.05†  (baseline-6wk*, PBM*)  *P*<0.05†  *(*baseline-6wk, *Control*)  ***Between group effects***  *P*>0.05  (any time points)  SFR  ***Within group effects***  *P*>0.05  (baseline-6wk, *PBM*)  *P*<0.05†  (baseline-6wk, *Control*) unstimulated SFR)  ***Between group effects***  *P*>0.05  (any time points)  OHIP-14  ***Within group effects***  *P*<0.05†  (baseline-6wk, *PBM*)  *P*<0.05†  (baseline-6wk, *Control*)  ***Between group effects***  *P*>0.05  (any time points) |
| **Sikora et at. (2018)**‡  RCT  BMS | *PBM*  n=22  *Control*  n=22 | 830 | Not specified | 100 | Chopped  800ms:1ms  (5 mm) | 12 | Not  specified | Weekly  2wk  (10) | Placebo | **OHIP-14** | No reported | Baseline  After treatment | Burning sites | OHIP-14  ***Within group effects***  *P*=0.153  (baseline-after*, PBM*)  *P*=0.302  (baseline-after, *Control*) |
| **Spanemberg et al. (2015)**  RCT  BMS | *PBM IR1W* n=20  *PBM IR3W* n=20  *PBM red*  n=19  *Control* n=19 | *PBM IR1W* 830  *PBM IR3W* 830  *PBM red*  685 | 0.028 | *PBM IR1W* 100  *PBM IR3W* 100  *PBM red*  35 | Continuous  (contact) | *PBM IR1W* 176  *PBM IR3W* 176  *PBM red*  72 | *PBM IR1W*  50  *PBM IR3W*  50  *PBM red*  58 | *PBM IR1W*  1/wk  10wk  (10)  *PBM IR3W*  3/wk  3wk  (9)  *PBM red*  3/wk  3wk  (9)  *Control*  3/wk  3wk  (9) | Placebo | **OHIP-14** | No reported | Baseline  After treatment  *Follow-up:*  8 wk  after treatment | 44 intraoral points  (tongue, buccal mucosa, labial mucosa, hard palate, soft palate, gums or alveolar ridge mucosa) | OHIP-14  ***Within group effects***  *P*=0.002†  (baseline-after, *Control*)  *P*<0.001†  (baseline-after, *IR1W*)  *P*<0.001†  (baseline-after, *IR3W*)  *P*=0.001†  (baseline-after, *Red*)  ***Between group effects***  *P*=0.021†  (after, *IR3W>Control*)  *P*>0.05  (pairwise comparisons) |
| **Sugaya et al. (2016)**  RCT  BMS | *PBM*  n=13  *Control*  n=10 | 790 | 0.03 | 120 | Scanning  (contact) | 6 | 50 | 2/wk  2wk  (4) | Placebo | **VAS symptoms** | No reported | Baseline  After each session  *Follow-up:*  d7-d14-d30-d60-d90 | Burning sites | VAS  ***Between group effects***  *P*=0.002†  (after 4 session, *PBM>Control*)  *P*=0.02†  (d90, *PBM>Control*)  *P*>0.05  (rest of time points) |
| **Valenzuela et al. (2017)**  RCT  BMS | *PBM I*  n=16  *PBM II*  n=16  *Control*  n=12 | 815 | 0.03 | 1000 | Continuous  (contact) | *PBM I*  133.3  *PBM II*  200 | *PBM I*  4  *PBM II*  6 | 1/wk  4wk  (4) | Placebo | **OHIP-14**  **Xerostomia severity test** | No reported | Baseline  2 wk  4 wk | Burning sites  10 points | OHIP-14  ***Within group effects***  *P*>0.05  (over time, *Control*)  *P*<0.001†  (over time, *PBM I*)  *P*<0.001†  (over time, *PBM II*)  ***Between group effects***  *P*=0.026†  (baseline-2wk, *PBM I-II>Control)*  *P*>0.05  (2wk-4wk)  Xerostomia  ***Within group effects***  *P*=0.083  (all groups, over time)  ***Between group effects***  *P*=0.091  (over time) |

RCT: randomized controlled trial; BMS: burning mouth syndrome; PBM: photobiomodulation; OHIP: oral health impact profile; SOB: secondary oral burning; ALA: Alpha-lipoic acid; SFR: salivary flow rate; SS: sjögren’s syndrome; HNC: head and neck cancer; RT: radiotherapy; VAS: visual analogue scale; IR1W: infrared laser weekly; IR3W: infrared laser three times a week.

†Level of significance (P<0.05).

‡Included in meta-analysis.

§Data has been calculated undirectedly.

GREY

**FIGURES AND TABLES LEGENDS**

**Figure 1** Flowchart PRISMA.

**Figure 2** Forest plot presenting the effect of Photobiomodulation (PBM) on the improvement of Quality of Life (QoL) measured by Oral Health Impact Profile (OHIP) in patients with burning mouth syndrome, compare with placebo; pre-post intervention data. Values on x-asis denote standardised mean differences. The diamond illustrates the 95% confidence interval of the pooled effects. Risk of bias legend: (A) Randomisation process; (B) Deviations from intended interventions; (C) Missing outcome data; (D) Measurement of the outcome; (E) Selection of the reported result; (F) Overall Bias.

**Table 1** Characteristics of 11 RCTs regarding PBM therapy for xerostomia and hyposalivation.

**SUPPLEMENTARY MATERIAL**

**Supplementary material 1** Medline Search strategy (Pubmed)

**Supplementary material 2** Sensitivity/precision analysis for each database.

**Supplementary material 3** Risk of bias graph with judgments about each topic, presented as percentages across all included studies.

**Supplementary material 4** Risk of bias summary with judgments about each item across included studies. (+)=Low risk of bias; (?)=Unclear risk of bias; (−)=High risk of bias.

**PRISMA 2009 Flow Diagram**



**Additional records identified through reference lists/automatic alert notification**  
(n = **2**)

**Full-text articles excluded, with reasons**  
(n =**10**)

Clinical entities not relevant = **3**

Study non-RCT = **2**

Registry clinical trial = **1**

Registry clinical trial already included full-text = **1**

Proceedings = **1**

Other language (Russian) = **1**

Outcome measures not relevant = **1**

**Records excluded**

Not relevant

(n = **201**)

**Studies included in qualitative synthesis**  
(n = **11**)

**Full-text articles assessed for eligibility**  
(n = **19**)

**Records screened by title and abstract**  
(n = **220**)

**Records identified through database searching**  
(n = **274**)

**Records after duplicates removed**  
(n = **220**)

## Identification

## Eligibility

## Included

## Screening

![Tabla

Descripción generada automáticamente con confianza media]()

**Supplementary material 1:**

**Medline Search strategy (Pubmed)**

((low-level light therapy[MeSH Terms] OR low-level light therap\*[All Fields] OR low level light therap\*[All Fields]) OR (photobiomodulation therap\*[tiab] OR LLLT[tiab] OR low level laser therap\*[tiab] OR low-level laser therap\*[tiab] OR low level laser treatment\*[tiab] OR low-level laser treatment\*[tiab] OR low level laser irradiation\*[tiab] OR low-level laser irradiation\*[tiab] OR low power laser irradiation\*[tiab] OR low-power laser irradiation\*[tiab] OR low power laser therap\*[tiab] OR low-power laser therap\*[tiab] OR laser biostimulation[tiab] OR laser phototherap\*[tiab] OR laser therap\*[tiab] OR laser treatment\*[tiab] OR low energy laser treatment\*[tiab] OR low-energy laser treatment\*[tiab] OR low energy laser therap\*[tiab] OR low-energy laser therap\*[tiab] OR low intensity laser therap\*[tiab] OR low-intensity laser therap\*[tiab] OR low intensity laser treatment\*[tiab] OR low-intensity laser treatment\*[tiab] OR phototherap\*[tiab] OR infrared laser[tiab] OR cold laser[tiab] OR cold laser therap\*[tiab] OR low level laser[tiab] OR low-level laser[tiab])) **AND** (dry mouth[tiab] OR hyposalivation\*[tiab] OR (xerostomia[MeSH Terms] OR xerostomia\*[All Fields]) OR mouth dryness[tiab] OR sjogren's syndrome[tiab] OR asialia\*[tiab] OR oral dryness[tiab] OR sjgren's syndrome[tiab] OR burning mouth syndrome[tiab] OR BMS[tiab] OR asialorrehea[tiab] OR stomatodynia[tiab] OR xerostomy[tiab]) **AND** (client\*[tiab] OR (patient[MeSH Terms] OR patients[All Fields]) OR inpatient\*[tiab] OR in-patient\*[tiab] OR outpatient\*[tiab] OR out-patient\*[tiab]) **AND** (randomized controlled clinical trial\*[tiab] OR randomised controlled clinical trial\*[tiab] OR (randomized controlled trial\*[Publication Type] OR randomised controlled trial\*[Publication Type] OR randomized controlled trials as topic[MeSH Terms] OR randomized controlled trial\*[All Fields] OR randomised controlled trial\*[All Fields]) OR clinical controlled trial\*[tiab] OR controlled clinical trial\*[tiab] OR clinical trial\*[tiab] OR random allocation[tiab] OR randomly allocated[tiab] OR allocated randomly[tiab])

**Supplementary material 2:**

Sensitivity/precision analysis for each database.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Databases | Total hits  retrieved | Relevant  hits retrieved | NNR | Unique hits | Sensitivity | precision |
| Medline | 20 | 9 | **2.22** | - | 90 | **45** |
| Scopus | 107 | 9 | 11.89 | - | 90 | 8.41 |
| WoS | 36 | 7 | 5.14 | - | 70 | 19.44 |
| Cochrane | 25 | 10 | 2.5 | 1 | **100** | 40 |
| CINAHL | 86 | 2 | 43 | - | 20 | 2.32 |
| TOTAL | 274 | 10\* |  | | | |

Number asterisked (\*) include total number of hits after duplicates removed.

NNR: Number Needed to Read (total hits retrieved/ relevant hits on a database).

Unique paper: relevant study retrieved from one database only.

Sensitivity: relevant hits retrieved / relevant hits retrieved TOTAL (%).

Precision: relevant hits retrieved / total retrieved (%).

Gráfico, Gráfico de barras

Descripción generada automáticamente **Supplementary material 3**

**Supplementary material** **4**