A Systematic Review of Treatment for Patients with Burning Mouth Syndrome

Huann Lan Tan[1,2], Jared G. Smith[3], Jan Hoffmann[4,5,#], Tara Renton[1,#]

[1)] Faculty of Dentistry, Oral & Craniofacial Science, King's College London, UK

[2)] Faculty of Dentistry, The National University of Malaysia, Kuala Lumpur, Malaysia

[3)] Population Health Research Institute, St George's, University of London, London, United Kingdom

[4)] Wolfson Centre for Age-Related Diseases, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[5)] NIHR-Wellcome Trust King's Clinical Research Facility/SLaM Biomedical Research Centre, King's College Hospital, London, UK

# JH and TR contributed equally to the manuscript.

Correspondence to:

Dr Jan Hoffmann
Wolfson Centre for Age-Related Diseases
Institute of Psychiatry, Psychology and Neuroscience
King's College London
London SE5 9PJ, United Kingdom
Tel: +44-3299-3106
jan.hoffmann@kcl.ac.uk

Abstract

Background: Burning mouth syndrome (BMS) is a chronic idiopathic intractable intraoral dysaesthesia that remains a challenge to clinicians due to its poorly understood pathogenesis and inconsistent response to various treatments.

Aim: This review aimed to study the short-(≤ 3 months) and long-term (> 3 months) effectiveness and sustainable benefit of different BMS treatment strategies and the associated side effects.

Materials and methods: Randomised control trial of BMS treatment compared with placebo or other interventions with a minimum follow up of two months were searched from the PubMed, Embase and Cochrane database (published till July 2020).

Results: Twenty-two studies were selected based on the inclusion and exclusion criteria and analysed. Nine categories of BMS treatment were identified: anticonvulsant and antidepressant agents, phytomedicine and alpha lipoic acid supplements, low-level laser therapy, saliva substitute, transcranial magnetic stimulation (rTMS), and cognitive behaviour therapy (CBT). CBT, topical capsaicin and clonazepam, and laser therapy demonstrated favourable outcome in both short- and long-term assessment. Phytomedicines reported a short- term benefit in pain score reduction. The pooled effect of ALA pain score improvement was low, but its positive effects increase in long term assessment.

Conclusion: A more significant volume on sample size, multi-centres, and multi-arm comparison of therapeutic agents with placebo and longitudinal follow-up studies is recommended to establish a standardised BMS treatment protocol. Further studies are required to assess the analgesic benefits of topical clonazepam and capsaicin, alternative medicines with neurodegenerative prevention capability and psychology support in treating BMS and reducing systemic adverse drug's reaction.

Introduction

Burning mouth syndrome (BMS) is defined as idiopathic orofacial pain with intraoral burning or dysaesthesia recurring daily for more than two hours per day and more than three months, without any identifiable causative lesions, with and without somatosensory changes in International Classification of Orofacial Pain, 2020 (1). BMS prevalence ranges from 0.1% to 3.9% and is primarily present in postmenopausal women aged between 50 and 70 (2,3). BMS commonly manifests as burning, prickling, tingling, itching or numbness affecting the tongue, lip, palate, gums and other oral mucosae (4). The pain intensity increases throughout the day and peaks in the late evening (5). Patients often complain of dysgeusia, xerostomia, altered sensation in the oral mucosa, and psychological issues such as anxiety and depression. The pathogenesis of BMS has been hypothesised to be associated with psychological disorders (6) and peripheral and central neuropathy (7), but at present, it is classified as idiopathic chronic pain (1). Diagnosing and managing patients with BMS remains a challenge to clinicians due to its poorly understood pathogenesis and inconsistent and limited response to various treatments. Besides, it has an exceptionally low spontaneous remission prevalence of 3-4% after five to six years of diagnosis (8). There are no global guidelines on BMS treatment, and published review articles included clinical studies with limited follow up periods (<2 months) (9-11). Based on the current universal ICOP criteria, the diversity of BMS patients underlying pain mechanism, and the difference evidence on short- and long- term benefit of treatment in BMS (11), we sought to conduct a systematic review on different therapeutic strategies for patients presenting with BMS, with the question 'which range of treatments have effective short (≤ 3 months) and long-term (> 3 months) outcomes in improving the pain symptoms in BMS patients? Parallel with the aim of providing a personalised treatment for each patient, the sustainability of a treatment efficacy and patients' compliance and response towards the therapy and its side effect should be consider.

Methodology

3

Search strategy

The study was carried out following the PRISMA guidelines (12). An electronic search on PubMed Medline (1946 to 1st July 2020), Embase Ovid (1980 to 1st July 2020), Cochrane Database of Systematic Reviews (1st July 2020) and Cochrane Central Register of Controlled Trials (CENTRAL) (1st July 2020) was conducted based on the combination of the following keywords: 'burning mouth syndrome or glossalgia or stomatodynia AND treatment or therapy or therapeutic or management'. This review includes all randomised and controlled clinical trials with a placebo published in the English language. The included studies should state that the diagnosis of BMS is based on the absence of local and systemic pathological contributing factors and have a minimum follow up of treatment of two months. This systematic review was registered in PROSPERO (Protocol ID: CRD42020160892). We also performed a manual search on all included clinical trials in published systematic review articles for any potentially relevant studies.

Study selection

The search results were screened based on the relevant title and abstract by two independent authors. Where information from the abstract was inadequate to allow a decision, a full report was obtained. The full text was obtained for articles fulfilling the inclusion criteria. Any disagreements were resolved by discussion between the authors, and the review authors were not blinded to articles' authorship. Studies meeting the inclusion criteria underwent data extraction and were evaluated for study risk of bias. The following data was obtained and recorded in a standardised proforma sheet on author and year of publication; study design or methodology; sample size and participant inclusion and/or exclusion criteria; types of intervention and follow-up time; the outcome and/or adverse effect from the intervention; statistical methods employed (Table 1).

Assessment of risk of bias

We used the Cochrane risk of bias assessment tool (13), which is based on seven main domains (Table 2). Each study was categorised based on the overall risk category and classified as low, unclear or high risk. The quality of all included articles was assessed using the GRADE (14).

Outcome Analysis

We analysed outcome data based on short term (≥2month to ≤ 3months) and long term (> 3months) changes in symptoms. The assessment method used in the included studies should be of equal measure. The standardised mean difference (SMD) in pain score (VAS) of treatment groups and placebo and their relative risk ratio (RR) for BMS pain improvement was recorded from the relevant studies with the 95% confidence interval (CI) where possible. Estimates of effect (and associated CI) were combined and pooled for studies reporting the same treatment.

Statistical analysis

Mean difference (MD) of the pre- to post-treatment VAS change scores were extracted from studies. For each study with comparisons between treatment and placebo at short term (≤ 3months) and/or long term (> 3 months), standardised mean differences (SMDs) of the VAS scores were calculated using pre-to-post-intervention change score (means) and post-intervention SDs (rather than change score SDs which were not provided in several studies). Means and/or standard deviations for baseline and post-treatment pain intensity were calculated for two studies based on the length of error bars in graphs and a ruler and two other studies using raw data (provided in papers). Continuous data were pooled using the Hedges g statistic as a formulation for the SMD under the fixed effects model. Relative risks (RRs) and 95% CI were calculated using the number of patients demonstrating improvement in VAS with reduction of VAS scores at post-intervention compared to the initial, according to Altman DG and Dore CJ, 1990 (15). Where zeros caused problems with the computation of the RR or its CIs, 0.5 was added to frequency cells (16,17). Where appropriate, RR data were pooled (under a fixed effect model). Formal meta-analyses were not performed in this review due to the

5

heterogeneity of included studies' methods and outcome data such as varying assessment times within short- and long-term testing periods, differences in treatment regime (e.g., timing or dosage of medication administration), different outcome assessments of burning or general pain improvement, and incomplete data (e.g., variance not reported).

Results

A total of 95 full text published articles were reviewed; 22 were included in this review (Table 1), and 73 were excluded (Table 3). Figure 1 shows the study selection flow process.

Characteristics of studies

All 22 included studies were randomised controlled clinical trials with one triple blinded study (participant, caretaker and assessor) (18), 14 double-blinded studies (19-32), four single-blinded studies (participants) (33-36), and three non-blinded studies (37-39). Three of the four single-blinded studies have a common concern with assessor blinding as they involved patient-reported outcomes (33,34,36). Fourteen (64%) studies described the method employed in generating the randomised sequence; online website or computer software, and randomisation tables, balls or blocks (18-21,23-25,27-29,31,33,35,38). Eight studies reported on examiners' allocation concealment (18,20,21,24,25,27-29). Five studies (22%) have a high risk of attrition bias (24,26,29,32,35), and eight studies (36%) have a high risk of reporting bias (20,22,24-27,31,32). In the reviewers' opinion, none of the studies was graded high, with two very low (38,39), 12 low (22,24,26,27,30-37) and eight moderate (18-21,23,25,28,29).

Twenty studies were randomised controlled trials (RCT) with placebo parallel-group comparison (18-29,31-38), and two studies were a comparison between different parallel cohort treatment groups (30,39). The 20 placebo-controlled randomised trials consisted of 16 trials with two-arm (18-22,24,26-29,31,32,35-38) (14 intervention versus placebo and two non-intervention versus intervention), one

trial with three-arm (23), and three trials with four arms (25,33,34) comparison between intervention and placebo. The remaining two non-placebo RCT were two-arm (30) and three-arm (39) trials investigating several different treatment interventions. Thirteen studies with a follow-up period between two and three months were categorised as short-term assessment (18, 21-26,29,31-33,35,37). Seven studies were reporting long term assessments (>3 months), ranging between 4 and 12 months (19, 22,23,31,33,36,37).

The total pool of treated participants was 623, with a wide age range from 43 to 89 years. All BMS participants were appropriately defined as having chronic pain for more than three months, with normal oral mucosa and absence of contributing local or systemic factors, except De Rivera Campillo R et al., 2010 (19) (duration of BMS was less than six months), Cinar SL et al., 2018 (39) (average duration of BMS was 17 days), Ottaviani et al., 2019 (31) (duration of pain was one month), and Bergdahl et al., 1995 (37) (no description on BMS duration).

The visual analogue scale (VAS) or visual numerical scale (VNS) of either 0 to 10 or 0 to 100 scores were the primary assessment tools in measuring post-therapy pain improvement (18,20,21,23,24,27-29,31,33-35,38) except Bergdahl J et al., 1995 (37) with a VAS scale of 1 to 7. Six studies used categorical changes in pain improvement as their assessment tool (22,23,25,26,32,33). Supplementary assessment tools such as the McGill Pain Questionnaire (21,23,35,36), faces scales (29), Orofacial Pain Clinic Questionnaire (EDOF-HC) (32) and Brief pain Inventory (BPI) (35) were used to evaluate pain intensity and associated characteristics further. Face scales classified patients' expression of happiness based on a pictured face scale of 0 to 5 (lower better). Secondary outcome assessment of participants' quality of health, anxiety and depression, and quality of sleep were evaluated using patient-reported questionnaires, such as 36-Short Form Health Survey (SF-36), Oral Health on Quality of Life (OHIP 14), Patient Health Questionnaires-9 (PHQ-9), Patient Global Impression of Change (PGIC), Clinical Global Impression for global Improvement Scale (CGC-Z), Hospital Anxiety and

Depression Scale (HADS), Beck Depression Inventory (BDI), Zerssen Mood Scale (ZMS), Hamilton Rating Scale (HRS), Psychometric Symptom Checklist-90-R (SCL-90-R), Medical Outcomes Survey (MOS) of Sleep Scale and Epworth Sleepiness Scale (ESS).

The substantial heterogeneity in the treatment methodology and regime, the follow-up time and inadequately reported statistical data precluded formal meta-analysis on the efficacy of a treatment in this review. However, a combined SMD VAS scores or RR of studies with similar interventions were pooled with 95% CI. Two studies without comparison with placebo (30,39) and another, which described outcomes using median values (27), were qualitatively analysed.

Effects of treatment

The effectiveness of various treatments and pooled efficacy for similar treatments for BMS between short- and long-term outcomes were shown in Figure 2 to 5, respectively.

Anticonvulsants

Clonazepam

The efficacy of clonazepam in reducing BMS pain symptoms was reported in two studies with oral (20,39) and one with topical administration (19).

Short term (2 months)

Treating BMS pain symptoms with daily oral systemic clonazepam 0.5 mg has shown favourable results of pain score reduction but was not statistically significant in the SMD analysis (SMD -0.63, 95% CI -1.56 to 0.29) (20). Despite the improvement in the taste, odour, and salivary flow rate, there were no statistically significant differences in improvement between clonazepam and placebo groups in taste (p=0.83) and salivary flow (p=0.03). Clonazepam did not improve patients' ZMS mood and BDI depression scores.

Long term (4 months and 6 months)

Administration of 2 mg clonazepam has been reported to reduce VAS score significantly at four months (MD -4.1, p<0.001) (39). Eight of the 25 participants developed side-effects such as dizziness (n=4), transient diarrhoea (n=2) and myalgia (n=2) with the use of clonazepam. Within the clonazepam group, 70% of patients described an improvement in pain intensity, and three participants were completely asymptomatic after six months of daily rinsing with 0.5 to 2.0 mg clonazepam (19). The application of topical clonazepam significantly decreased patients' VAS score (MD -4.7) (SMD -1.06, 95% CI -1.58 to -0.54) in comparison to placebo than oral ingestion clonazepam (20) (MD -3.2) (SMD -0.63, 95% CI -1.56 to 0.29) and no significant difference in the total number of tablets dissolved in the mouth as a topical application between both clonazepam and placebo groups. Six months of clonazepam rinse statistically significantly reduced pain scores by 13-fold (RR 13.0, 95% CI 3.35 to 50.39). Five clonazepam participants reported sleepiness as adverse effects, but they were not suspended from the trial.

Gabapentin

Short term (2 months)

Patients receiving 300 mg gabapentin has shown a similar result to alpha lipoic acid (ALA), with half of the total number of patients evidencing improvement in pain or total pain recovery (25). A more than three-fold likelihood of positive change relative to placebo were reported with the use of gabapentin in the short-term assessment of 20 BMS patients (25) (RR 3.33, 95% CI 1.58 to 7.02). It is associated with approximately a five-fold likelihood of decrease in pain levels compare with placebo if combined with ALA (RR 4.67, 95% CI 2.40 to 9.09) (25).

Pregabalin

Long term (4 months)

At four months of assessment, 150 mg pregabalin showed a significant reduction in VAS scores (MD -4.7, p<0.001) (Cinar, 2018). Six of the 25 participants had side effects such as increase in appetite (n=3), vertigo (n=1), mild nausea (n=1) and diarrhoea (n=1).

Antidepressants

Trazodone

Short term (2 months)

Administration of 100 mg trazodone daily for the first four days followed by 200 mg for eight weeks significantly decreased patients' VNS pain intensity against baseline (MD -13.9, p<0.01), but there was no significant difference with the placebo group (SMD -0.06, 95% CI -0.72 to 0.59; RR 0.95, 95% CI 0.61 to 1.49) (21). If the assessment was based on the 'Patients' Global Assessment of Improvement' evaluation, trazodone and placebo groups reported improvements in pain intensity of 73% and 76%, respectively, and were not significant (p>0.05). One patient in the trazodone group reported a worsening of symptoms. Both the trazodone and placebo groups significantly improved their BDI depression scores (p<0.01). The most common side effects were dizziness and drowsiness, with seven patients dropping out due to dizziness. Other side effects included abdominal pains, headache, palpitation, tremor, xerostomia, and urinary incontinence.

Citalopram

Short term (11 weeks)

The use of citalopram 10 mg daily followed by an increment to 20 mg after one week showed an improvement of VAS score of 87.45% (MD: -7.8, p<0.001) (30). However, comparison with crocin reported no significant difference between their post treatment VAS scores (p=0.98). The Hamilton questionnaires analysis revealed a significant reduction of depression and anxiety scores, with an average recovery percentage of improvement of 30.57% (SD 15.81) and 15.44% (SD 11.86), respectively. There was no significant difference in comparison between both groups in depression

(citalopram: 19.4, SD 4.65; crocin: 19.0, SD 3.97, p=0.76) or anxiety (citalopram :18.6, SD 5.11; crocin:18.0, SD 4.38, p=0.76).

Phytomedicine

Topical Capsaicin

Short term (2 months)

Rinsing with 250 mg of chilli powder emulsified in 50 ml water with a dose concentration of 3.54 µg⁄ml capsaicin has been reported to induce a significant reduction in VAS score (MD -3.2, p<0.01) with 76% of participants reporting an improvement in symptoms, but one patient-reporting a worsening (33). Capsaicin provides an immediate short term pain relief (SMD -1.49, 95% CI -2.35 to -0.63) and is statistically significant with 21 times better than placebo (RR 21.00, 95% CI 1.35 to 326.97). Topical capsaicin has shown a better clinical pain management outcome than oral ALA and lysozyme lactoperoxidase, despite no statistically significant VAS difference in intergroup comparison.

Long term (4 months)

Capsaicin showed superiority in maintaining VAS score reduction in long term (MD -2.9, p=0.03) compared to lysozyme-lactoperoxidase, boric acid rinse and ALA (33). It also demonstrates sustainable benefit in long term administration (SMD -1.09, 95% CI -2.11 to -0.06) (33). It is 13 times better than placebo but not statistically significant (RR 13.00, 95% CI 0.84 to 201.27). An improvement in pain intensity was reported by 67% of participants, while one patient remained the same, reported worsening of pain. No adverse effect was noted during the trial.

Ultramicronised Palmitoylethanolamide (umPEA)

Short term (2 months) & long term (4 months)

Ottaviani et al., 2019 revealed a short-term (60 days) benefit with 1200 mg/day umPEA in BMS patients (SMD -0.70, 95% CI -1.39 to -0.01) but declining pain relief at four months (SMD -0.26, 95%

CI -0.94 to 0.41) compared to placebo group (31). There were no side effects observed in patients treated with umPEA.

Herbal Catuama

Short term (3 months)

Catuama shows promising VNS (0-10) score reduction results compared to placebo with a minimal adverse effect of sleep alteration observed in the study (SMD -0.68, 95% CI -1.21 to -0.16) (29). Catuama shows a greater alleviation of patient symptoms with a lower faces scale score at both 8 and 12 weeks than placebo (p≤0.001). The mean reduction of the face score were 1.6 and 1.5 for 8 and 12 weeks, respectively, while there were no changes in participants' happiness in the control group with a similar mean reduction faces scale scores of 0.6 at 8 and 12 weeks. The majority of patients tolerated the treatment well, with none of the patients in the test group reporting xerostomia. The side effects reported by patients that took Catuama included somnolence and weight gain (n=1), insomnia (n=1), and exacerbation of the pain symptoms intensity in the first week of treatment (n=2). A drop out of eight (21.1%) participants in the treatment group, and four (11.8%) in the placebo group were reported.

Hypericum Perforatum

Short term (3 months)

At the end of 12 weeks of therapy, there was a reduction in the number of oral mucosa burning sites and improved ability to cope with the burning pain, there was no statistically significant difference with the placebo group (SMD -0.23, 95% CI -0.87 to 0.41) (28). The HAD questionnaires showed that approximately 50% of patients in both treatment and placebo groups evidenced better coping ability on their pain symptoms at the end of the trial. One participant developed a severe headache in the fifth week of active therapy (28).

Crocin

Short term (11 weeks)

Crocin showed a significant reduction in VAS score (MD-7.8, p<0.001) and has a similar improvement 87.5% of burning mouth score as citalopram (30). A significant improvement in depression and anxiety scores by 30.79% (SD 13.24) and 15.40% (SD 13.98), respectively, were reported. Crocin displayed similar effects as citalopram in treating burning pain, depression and anxiety.

Lycopene enriched extra virgin oil (LVO)

Short term (3 months)

A combination of topical spray and swallowing of 900 ppm LVO daily for 12 weeks led to a significant reduction in the median pain score (Median Difference -3.0, p<0.001) and burning (Median Difference -1.0, p=0.003) compared to baseline, but there was no significant difference (p=0.99) when compared with the placebo group (27). Evaluation of SP-36 and OHIP-14 questionnaire scores showed no difference in changes to quality of life between treatment and placebo groups. HAD anxiety scores did not differ between treatment and placebo groups or significantly change throughout the trial period. The cholesterol and triglycerides levels were not remarkably raised after 12 weeks of LVO administration.

Alpha lipoic acid (ALA)

Short term (2 months)

Four ALA trials (22,25,26,33) showed promising pain reduction in comparison to placebo during short term assessment (Femiano & Scully, 2002: RR 2.42, 95% CI 1.55 to 3.77; Lopez D'alessandro, 2011: RR 3.67, 95% CI 1.78 to 7.54; Palacios-Sanchez, 2015: RR 2.32, 95% CI 1.20 to 4.48; Marino, 2010: RR 17.0, 95% CI 1.08 to 268.86) while two did not (Carbone,2009: SMD -0.06, 95% CI -0.75 to 0.64; RR 0.95, 95% CI 0.33 to 2.76; Lopez Jornet , 2009: SMD 0.56, 95% CI -0.10 to 1.22) (23,24). The pooled ALA suggested a more than double increase in likelihood of pain improvement (RR 2.44, 95% CI 1.57 to

3.78, p<0.001) compared to placebo (22,23,25,26,33). However, there were no significant changes in the pooled ALA VAS scores (SMD -0.17, 95% CI -1.08 to 0.75, t -0.36, p=0.72), reflecting the heterogeneity across studies (23,24,33). One patient had to discontinue treatment during the trial due to gastrointestinal upset such as nausea, dyspepsia and pyrosis (24).

Long term (4 months and 12 months)

Two studies (23,33) assessed the persistence of the observed improvement for two months after discontinuation of therapy and described a stable decrease of VAS score (Carbone, 2009: MD -1.8, SD 3.19, p=0.01; Marino, 2010: MD -1.8, p>0.05). Long term used of ALA did not result in any statistically significant improvement over placebo, suggested by the pooled VAS mean score changes (SMD -0.40, 95% CI -0.95 to 0.15, p=0.15) (23,33) and the likelihood of improvement (RR 3.66, 95% CI 0.55 to 24.45, p=0.18) (22,23,33).

A study comparing ALA 600 mg with two other drugs (clonazepam and pregabalin) showed no significant improvement at four months of assessment (MD -0.72, p>0.05). Three out of 25 patients reported side effects, including mild nausea (n=2) and myalgia (n=1) (39). A one-year follow-up showed a sustained effect on pain intensity in 73% of patients. In this study, patients with signs of improvement within the first four months of treatment were given an extended treatment of one month ALA 600 mg (22).

ALA and Gabapentin

Short term (2 months)

A combination of 600 mg ALA and 300 mg gabapentin in a randomised, double-blind clinical trial described a notable pain reduction, with 70% of patients demonstrating a partial or complete improvement in pain intensity compared to 15% in the placebo group (25). The combination use of

ALA and gabapentin was five- fold likelihood (RR 4.67, 95% CI 2.40 to 9.09) (p<0.001) of decrease pain intensity while ALA only has four times likelihood beneficial effect (RR 3.67, 95% CI 1.78 to 7.54).

ALA and Vitamins

Short term (2 months) and long term (4 months)

Combining vitamins such as vitamin C, PP, E, B6, 2,1, 12 and folic acid with 800 mg ALA did significantly improve VAS score (MD -1.0, SD 1.83, p=0.047) and a further reduction in VAS score was noted two months after termination of treatment (MD -1.8, SD 3.19, p=0.047) (23). However, there was no significant difference between ALA and vitamins (SMD 0.21, 95% CI 0.44 to 0.85) (SMD -0.15, 95%CI -0.79 to 0.50) compared to ALA monotherapy (SMD -0.06, 95%CI -0.75 to 0.64) (SMD -0.23, 95%CI -0.93 t0 0.47) or placebo in both short (p=0.60) and long-term assessment (0.79). ALA as a monotherapy led to a higher reduction in VAS score at two months (MD -1.6, p=0.013) but no statistically significant difference compared to placebo (p=0.60) compared to baseline, but there was no significant difference between the ALA (monotherapy), ALA and vitamin (combination) and placebo groups. No adverse effects were reported in the study (23).

Melatonin

Short term (2 months)

A cross-over clinical trial involving intervention with a high melatonin dosage (12 mg/day) did not provide pain relief (SMD 0.24, 95% CI -0.39 to 0.87; RR 1.18, 95%CI 0.31 to 4.43) and sleep score improvement compared to placebo (18). Ten participants reported no changes in symptoms, and one participant reported worsening of symptoms. The value of VAS score and serum plasma melatonin concentration was negatively associated, but it was not statistically significant (p>0.05). Two patients in the melatonin group demonstrated a positive correlation between decreased VAS scores and increased sleep hours. The Hamilton rating scale for anxiety (HAM) assessments scores was always higher in the melatonin group than placebo, with a statistically significant decrease in the melatonin

group's anxiety score (p<0.05). An approximate two-fold of patients reported sleep impairment using melatonin (n=10, 62.5%) compared to placebo (n=6, 37.5%). Mild daytime sleepiness was seen in melatonin and placebo groups, with high ESS scores but not significant between them (p>0.05). The main adverse effect of melatonin that leads to the discontinuation of treatment on four patients were heavy tremor, sexual disturbances, blurred vision, severe heavy headiness. Four patients were dropped from the study due to lack of efficacy, pain improvement, and follow-up loss.

Low-level laser therapy (LLLT)

Short term (11 weeks)

A significant reduction in pain score by three to five units was observed in the study using the red (p=0.13) and infrared laser (IR1W p=0.004 and IR3W p<0.001) (34). The red laser group (SMD -0.47, 95% CI -1.13 to 0.18) did not demonstrate a significant difference from the control group, but both IRW1 (SMD -0.80, 95% CI -1.46 to -0.14) and IRW3 (SMD -1.14, 95% CI -1.83 to -0.45) showed a statistically significant difference control group (34). No side effects were noted from the laser therapy.

Long term (4 months)

A recent trial has suggested the advantage of photobiomodulation in treating orofacial neuropathic pain, including BMS with a significant 4.5-fold likelihood of pain reduction in comparison to placebo (RR 4.50, 95% CI 1.28 to 15.81) and a more than 1-point decrease in VAS (SMD -1.12, 95% CI -2.10 to -0.15) (36), but no improvement in patients' psychology and quality of life. There was no significant improvement in McGill Pain scores, patient oral health quality scores (OHIP), physical and emotional scores (SF-36) and sleepiness (ESS). However, there was a significant decrease in SCL-90-R interpersonal sensitivity, somatisation, and anxiety between photobiomodulation group and placebo group (p=0.04). No adverse effects were reported.

Saliva substitutes

Topical Lysozyme lactoperoxidase (Biotene)

Short term (2 months) and long term (4 months)

Lysozyme lactoperoxidase (Biotene) rinse was prescribed to BMS patients diagnosed with xerostomia (33) and reported a decrease in pain score of 1.7 unit during short term assessment (SMD -0.93, 95% CI -1.72 to -0.13) but no advantage over placebo was seen in long term assessment (SMD -0.73, 95% CI -1.72 to 0.26). A 13-fold (RR 13.00, 95% CI 0.80 to 210.82) and nine-fold (RR 9.00, 95% CI 0.55 to 146.12) likelihood of pain reduction compared with placebo was observed in both short- and long-term analyses (33).

The lubricating rinse lysozyme lactoperoxidase significantly reduced the VAS score (MD -1.7, p=0.01), but there was no significant difference between lysozyme lactoperoxidase with capsaicin rinse and oral ALA, respectively (33). The pain score remained unchanged in 57% and 55% of patients in both short and long-term assessment.

Topical Urea

Short term (3 months)

Statistical analysis showed no statistically significant difference between the application of 10% urea for three months and placebo group (p=0.34) (RR 0.95, 95% CI 0.50 to 1.80) (32). There is no difference in pain intensity after treatment (p=0.88), although clinically 58.3% of patients demonstrated a reduction in pain intensity.

Transcranial magnetic stimulation (rTMS)

Short term (2 months)

Ten days of 30,000 pulses of rTMS therapy over the left GDLPFC significant reduced VAS score (MD: -3.1, p=0.002) with 75% of patients reporting a decrease in pain intensity of more than 50% compared

to baseline (35). There was a significant difference compared with placebo (MD: -2.8, p=0.005) (SMD -0.33, 95% CI -1.25 to 0.60). There was a significant improvement in sensory SFMPQ in the rTMS group (MD -4.84, p=0.002) but no difference in the SFMPQ affective scores and present pain intensity. PGIC and CGO-I assessments described positive changes from the patient in the rTMS group. There were no significant changes in patient mood based on PHQ-9 (MD 5.59, p=1.00).

Tongue protector

Short term (2 months)

The hypothesis of wearing the tongue protector to prevent continuous irritation of tongue on teeth or denture has a statistically significant difference in improvement in VAS score between wearer (MD -3.6) and non-wearer with habitual avoidance reminder (MD -1.4, p<0.001; SMD -1.15, 95% CI -1.76 to -0.54) (38). Participants did not show any improvement in the depression and anxiety score. There was a significant improvement in patient quality of life-based on OHIP-49 and SF36 assessments.

Cognitive therapy

Short term (12 -15 weeks) and long term (6 months)

At the end of weekly behavioural therapy for 12 to 15 weeks, patients reported a significant improvement in their pain score for both short- (SMD -2.16, 95% CI -3.09 to -1.24) and the long-term effects were sustained over six months post-treatment: (SMD -3.38, 95% CI -4.53 to -2.23) (37). There were statistically significant changes between the therapy and the placebo group (p<0.001).

Discussion

At present, there is no definitive curable treatment for BMS. Its aetiology remains uncertain with various suggested pathogenesis such as peripheral and central neuropathy disorders, psychological disorders, changes in gonadal, adrenal and neurosteroid levels, a dopamine D2 receptor (*DRD2*) 957C>T genotype and the association between BMS and other neurological diseases such as

Parkinson's disease (40-43). BMS treatment primarily aims at eliminating the painful burning dysaesthesia. Phenotyping BMS patients' aetiology could achieve this based on their clinical histories and responses toward various treatments. In this review we discuss nine BMS therapies: anticonvulsants (19,20,25,39), antidepressants (21,30), phytomedicines and food supplements (18, 22-29,31-33), lower-level laser therapy (34,36), saliva substitute (32,33), transcranial magnetic stimulation (35), oral appliances (38) and cognitive behavioural therapy (37).

Preceding systematic reviews included clinical trials of two weeks follow up assessment results. It is crucial to have a more extended review period of patients' responses towards the therapy, the sustainability of the treatment effects and the possible side effects before considering that a treatment has been effective. Hence, to ensure sufficient, sustainable benefits of the treatments, this review includes studies with a minimum follow of two months and divided them into short term (≤3 months) and long term (>3 months) treatments (11).

The majority of the included studies had small samples sizes. The diversified BMS patients' characteristics such as presence or absence of psychological disorders, taste disturbance, and xerostomia make recruitment for a larger homogenous sample group difficult in a clinical trial. The concurrent use of psychotherapeutic drugs or therapies and anti-inflammatory analgesic medications in patients may influence the presentation of the BMS population trials due to the ambiguity whether these psychological disorders preceded BMS (21,26,32,35,38).

Anticonvulsant

Clonazepam

Both oral ingestion and topical application of clonazepam have showed a favourable result on BMS pain relief up from two to six months (19,20,39). The association of peripheral or central nervous system in BMS pathogenesis explained the use of antiepileptic and antidepressant drugs. Continuous

nociceptive peripheral neuropathy input will eventually lead to central sensitisation and changes. Pharmacological drugs such as clonazepam demonstrated their analgesic ability by inhibiting neurological transduction and transmitting the pain signal. Clonazepam, a benzodiazepine anticonvulsant drug, acts as an agonist modulator on GABA-A receptors and activates the descending pain inhibitory pathway of the peripheral (PNS) and central nervous system (CNS) by facilitating the opening of the chloride channel. It antagonises the neuron hyperexcitability transmission by generating a continuous hyperpolarisation, thus preventing depolarisation and post deafferentation neuronal firings (44). GABA-A receptors are found in the oral mucosa, mandible, palate, salivary gland and taste pathway. GABA agonist could reverse the dysfunction of peripheral chorda tympani nerve and taste loss in BMS patients (45). Clonazepam could provide fast and continuous pain relief due to its rapid absorption and 90% bioavailability of clonazepam within one to four hours after oral administration and its long half-life of 30 to 40 hours.

Meanwhile, intraoral topical clonazepam has shown to be superior to oral ingestion in providing much rapid pain analgesia but a shorter duration of action. Patients reported rapid positive effects within 10 minutes upon dissolving the clonazepam tablet intraoral and recurrence of pain in three to four hours (19). The topical clonazepam route is simple with a rapid and shorter duration of action, which allows repetitive used and lower risk of common systemic adverse effects such as drowsiness, dizziness, and unsteadiness. It allows patients to have better self-control on the needs of pain relief magnitude in their daily activities. Inevitably, some of the topical clonazepam will be absorbed systematically through the oral mucosa and affect the CNS pain modulation. This is reported in a study assessing patient's post topical clonazepam serum concentration was similar between immediate five hours post sucking 1mg clonazepam tablet and sucking the tablet three times daily for 14 days (46).

The use of amitriptyline, a tricyclic antidepressant, commonly used to treat chronic neuropathic pain, has not been widely mentioned in BMS studies. This may be the result of the frequent xerostomia induced by amitriptyline that aggravates the pre-existing BMS-related xerostomia. A retrospective

study has reported a more superior rapid decrease of VAS pain scores outcome of clonazepam drops (n=23) than amitriptyline drops (n=16) at six weeks but no statistical difference between them (47).

Gabapentin & Pregabalin

Gabapentin and pregabalin have been the favourable drug choice in treating neuropathic pain conditions such as diabetic neuropathy, and postherpetic neuralgia due to is hepatic safety profile (48). The similar advantages in BMS pain were achieved with the used of gabapentin and pregabalin in short- and long-term assessment (25,39). Gabapentin mediates pain attenuation by binding to the α2δ-1 subunit of the voltage calcium channels and inhibit the release of neurotransmitter such as glutamate, CGRP and substance P, the development of chronic pain (49,50), which correlates BMS as a neuropathic pain that may involve both central and peripheral mechanisms. The benefits of gabapentin in BMS with peripheral neuropathy disorders may suggest using adjunct dietary supplements such as ALA to enhance the pain attenuation without increasing the synthetic drug's needs. However, a more extensive sample size study is recommended to test the efficacy of gabapentin and its adverse effects. Cinar et al., 2018 compared the use of systemic pregabalin (150 mg) with clonazepam (2 mg), and both drugs show similar significant efficacy in reducing pain score (39). A third of patients in both study groups had common adverse effects, but no patients withdrew from the study. The absence of a placebo group in the study failed to give a definitive superiority outcome between pregabalin and clonazepam (39).

Antidepressants

BMS has been strongly associated with depression and anxiety, and the lack of clarity between them in unsettling. This neurophysiological mechanism in BMS was shown in functional magnetic resonance imaging (fMRI) (51) and quantitative somatosensory testing (QST) study (52). fMRI study has reported an increase in the region's functional neural activity regulating depression and anxiety in BMS patients (51). It is known that chronic anxiety and depression may disturb neuroprotective steroid productions

(53). As pain could be a somatic trait, the use of antidepressant has been suggested the role of anxiety and depression in BMS pathogenesis.

Trazodone

Trazodone is a second-generation antidepressant that has been considered a multifunctional drug and acts as a serotonin reuptake inhibitor. Trazodone has been used in treating anxiety and pain symptoms, including fibromyalgia (54). However, in this review, trazodone use did not significantly affect pain reduction and had a high placebo effect. The reported high adverse effects on dizziness and drowsiness limit its use (21).

Citalopram

Citalopram has shown to be able to reduce pain intensity (30). A review of SSRIs such as zimelidine, sertraline, citalopram, paroxetine, and fluoxetine has suggested it for the treatment of chronic pain conditions (55). The SSRI citalopram has similar antidepressant and analgesic properties to tricyclic antidepressants but with significantly fewer side effects and better tolerability (56). Serotonin is a neurotransmitter that plays a role in both central and peripheral nociception and mood regulation. SSRI inhibit serotonin's reuptake and prolong its availability in the synaptic cleft. There was inconclusive effectiveness in treating chronic pain with SSRIs. Inconclusive results were observed from various studies on its use for chronic somatoform pain and fibromyalgia. As there is no placebo group in comparing the efficacy of citalopram in reducing burning mouth and less than 50% of patients recovered from depression and anxiety, there is limited evidence to support its use (30). Clinical trials with better methodology and low-risk bias are needed to conclude the effect of SSRI as a treatment for chronic pain conditions.

Phytomedicine

The perspective of using herbal medicine or phytomedicine has been established and increased in primary health care (57). The efficacy of phytomedicines such as capsaicin, herbal catuama, umPEA and hypericum perforatum have demonstrated their analgesia ability, with capsaicin having a tremendous number of patients in responding to it. Through well-designed randomised control trials and observational studies, phytomedicine has a tremendous future to be used solely or adjunct therapy in treatment therapeutic strategies and products (58).

Capsaicin

Capsaicin has shown to be an effective pain desensitiser especially with the oral topical application up to four months (33). Transient receptor potential vanilloid-1 receptors (TRPV1) are found in the PNS and CNS (59). The numbers of TRPV1 receptors are significantly increased in the mucosa of BMS patients' tongue (60). Activation of TRPV1 at the peripheral terminal fibre endings leads to the release of neuropeptides such as substance P, neurokinin A (NKA) and calcitonin-gene-related peptide (CGRP) that contributes to the onset of hyperalgesia pain and inflammation. Local capsaicin application activates the TRPV1 and modulates the nociceptive transmission of pain impulses from the peripheral stimulation site to the central nervous system by blocking axonal transportation, depleting neuropeptides, and loss of membrane action potential. Hence, capsaicin-induced analgesic effect by desensitisation of the nociceptive fibre (61-62), which is a reversible process (63). The used of topical capsaicin have been suggested in neuropathic pain, such as postherpetic neuralgia and painful HIV associated polyneuropathy (64-66) but not inflammatory pain such as osteoarthritis (67).

 A study showed no difference between systemic and topical capsaicin efficacy in BMS (68). However, gastric pain limits systemic capsaicin use (68). The use of topical capsaicin rinse is recommended in BMS due to its rapid action and no reported adverse effects as seen in other synthetic drugs. However, there are no known risks of long-term repeated rinsing of capsaicin, especially in the oral cavity mucosa innervation. Patients should be warned of the initial increase in burning pain induced by

topical capsaicin rinse or application followed by the discharge in the C and Aδ nociceptive fibres, but this effect is limited, of short duration and followed by pain relief. Cutaneous site pre-treatment with anaesthetic cream has been used clinically to reduce the capsaicin patch induced treatment discomfort in patients with peripheral neuropathic pain (69). Hence, a possible hypothetical proposition of a mouth rinse mixture containing both capsaicin and lidocaine may mask this initial burning pain and enhance pain relief effectiveness.

Ultramicronised palmitoylethanolamide (umPEA)

There is a mere reduction of pain score with umPEA and its effect did not sustain (31). Systemic administration of PEA elicits anti-inflammatory, antinociceptive, and neuroprotective effects, both in vivo and in vitro (70,71), as well as in man (72,73). Neurodegeneration could occur due to inflammatory reactions and activation of immune cells. Microglia facilitates the CNS's inflammatory response, and white mast cells coordinate PNS inflammation. umPEA is an endogenous fatty acid that suppresses the discharge of proinflammatory mediators from mast cells and microglia during inflammation, thus preventing neuronal injury and chronic pain. A meta-analysis study has reported umPEA as a novel treatment in managing chronic neuropathic pain caused by neuroinflammation (74). A study of 40 days umPEA has reported positive benefit in diabetic or traumatic peripheral neuropathic pain (75). The novelty of umPEA efficacy as a primary or adjunct treatment in BMS should be further studied with a larger cohort and follow up period for its sustainability.

Herbal Catuama

Three months used of catuama has shown a significant reduction in BMS pain score (29). Catuama is a herb commonly used for mental and physical exhaustion. It has been shown to have antidepressant, antinociceptive and vasorelaxant actions in animal models by acting on the dopaminergic, serotoninergic and opioid pathways and reducing the inflammatory nociception in animal models (76). It is thought that catuama may alleviate the burning pain based on the possible BMS aetiologies of

psychologic and neuropathic disorders. A more extended observation on the use of catuama is suggested to ensure its long-term adverse effects and suitability as a pain relief.

Hypericum Perforatum

The short-term use of hypericum perforatum in BMS has shown a favourable outcome but not significant to placebo (28). Hypericum perforatum (St. John's wort extracts) has been used as an antidepressant in mild to moderate depression, anxiety and sleep disorders (77) and may be beneficial to BMS patients as they frequently experience emotional and mood distress, in which anxiety and depression could be the primary or secondary event. Several active extracts in hypericum perforatum have a strong affinity for γ-aminobutyric acid (GABA), adenosine, serotonin 5HT1 and benzodiazepine receptors, and acts as monoamine oxidase inhibitors (MAOI) (78). Its action as an MAOI prevents the reuptake of norepinephrine, serotonin and dopamine neurotransmitters from the brain that has been responsible for the beneficial antidepressant effects. As a GABA agonist, it induces a temporary hyperpolarisation of the nervous membrane and ensuing desensitisation and inhibition of neurotransmission, which provides anxiolytic and analgesic effect (79).

Hypericum perforatum rarely causes any adverse drug reactions, except for dizziness and is usually well tolerated by the elderly (80). It has comparable efficacy and safety compared to SSRIs in patients with mild to moderate depression (81). However, there is inadequate evidence on its long-term efficacy and safety, especially in patients with severe depression or suicidal risk.

Although it is relatively safe, clinicians should be alerted on prescribing hypericum perforatum and other medications as it may elicit severe clinical adverse drug interaction effects. Hypericum perforatum activates the cytochrome P450 enzymes that are involved in drug metabolism, and reduced the drug plasma concentration and potency; such as warfarin (risk of thrombosis), cyclosporin (risk of transplant rejection), oral contraceptives (unintended pregnancy), anticonvulsant

(uncontrolled seizures), digoxin (heart arrhythmia), theophylline (poor asthmatic control), HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (diminution in HIV suppression) (82). Caution should be taken in combining hypericum perforatum with other antidepressants drugs as it increased the serotonergic effects in serotonin (5-HT1d) receptor agonist drugs (triptans) and selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (82,83).

Crocin

Crocin is a carotenoid chemical compound found in the flowers crocus and gardenia and is responsible for the saffron colour. Crocin prevents neuroinflammation and neurodegeneration by decreasing oxidative stress and cell death (84) by inhibiting microglial activation and suppressing inflammatory cytokine production (85). Microglia dysfunction contributes to the disturbance in their protective regulator function on neuroinflammation stimuli and generates an imbalance of reactive oxygen species (ROS) homeostasis and antioxidant system, creating oxidative stress (86,87). Oxidative stress is associated with neurodegeneration through is several cascades of deleterious events on the cells, causing lipid peroxidation, protein oxidation and mitochondrial DNA damage, and mutations (88). The accumulated increased oxidative stress in the aged brain has been thought to be a possible aetiology of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. There have been reports on BMS occurrence in a patient with Parkinson's disease (89,90), but there is no study on dysfunction microglia and mitochondria and the oxidative stress in BMS patients. The brain is much more vulnerable to this oxidative stress due to its high oxygen demand and lipids' vital role in maintaining neuronal function (91). Neuroprotective effects of crocin have been shown in an experimental animal model (84), but not in more extensive human clinical trials on its long-term safety and benefits. This review shows a significant improvement in crocin pain score but no significant superiority over citalopram (30). A three-arm- study design with placebo control group comparison is advised to compare crocin and citalopram's superiority.

Lycopene and Virgin olive oil (VOO)

Lycopene is naturally found in red carotenoid pigmented food, such as in tomatoes. It has antioxidant, anti-inflammatory and anti-apoptotic properties. These benefits have been seen in reducing cancer and cardiovascular risk with the consumption of lycopene and VOO (92,93). Combination of lycopene and VOO are thought to provide a synergistic effect of antioxidative and anti-inflammatory mechanisms. The ingestion of lycopene with olive oil will increase bioavailability (94). The application of topical lycopene and VOO may protect the oral mucosa's peripheral neurons from oxidative stress, while VOO provides a lubricant effect. However, lycopene and VOO are not superior to placebo in improving pain score and health quality (27).

Alpha lipoic acid (ALA)

ALA is the most studied treatment in BMS. Although the VAS findings from the pooled ALA analysis suggested there was no significant reduction in pain intensity of relative to placebo treatment, a significantly higher proportion of patients reported pain reduction with ALA. As such, it suggests ALA as a treatment for BMS, but the evidence is not conclusive due to the variability of the studies treatment regimens and short- and long-term studies results (9,10,11).

ALA is a naturally occurring compound found in the body and vegetables such as tomatoes, potatoes, broccoli, and brussels sprouts. It acts as an enzymatic cofactor for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes in glucose and lipid metabolism. ALA is a robust universal antioxidant and can chelate and remove heavy metals from the body. Thus, it reduces oxidative stress-induced inflammation and damage to the nerve. ALA's advantages and safety were demonstrated in the treatment of diabetic polyneuropathy pain and paraesthesia by preventing nerve fibre degeneration (95,96). Hence, the possible goal of administering ALA in BMS patients is to treat patients with peripheral neuropathy as the pathogenesis. The bioavailability of oral ALA is strongly

affected by its formulation and its regime due to its reduced solubility and stomach instability. ALA in liquid form is preferred over solid for better absorption and should be taken premeal. Age influences the bioavailability of ALA. Patients aged above 75 years have better absorption rates than 18 and 45 years, but there was no difference in gender (97). As BMS is commonly occurring in the fifth to seventh decade of age, ALA may be a beneficial adjunct supplement to ease the pain. In this review, the mean age reported ranged between 45 to 67 years.

ALA and gabapentin have shown a superior result, with mild adverse effects reported (25). Combined ALA use as an adjunct supplement to pharmacotrophic drugs may benefit the patients in minimising the drug's adverse effects by reducing the prescribed frequency and dosage. However, studies with larger sample sizes and longer follow-ups of a minimum of six months with better methodology design should be conducted to validate the use of ALA.

Melatonin

There was insufficient evidence on the benefit of melatonin in BMS. The relationship between pain and sleep are inextricable in which poor sleep quality is a risk factor for chronic pain development, and pain disrupts sleep pattern (98). Melatonin is a neurohormone that regulates the circadian biological rhythms. Melatonin has antioxidant, anti-inflammatory, anticancer, anxiolytic and antinociceptive activities (99). It has shown to reduce chronic pain in fibromyalgia (100) and temporomandibular joint disorders (101). The analgesic effect of melatonin in neuropathic pain has been demonstrated in animal models (102,103). The use of exogenous melatonin in neuropathic pain is controversial due to multiple complex analgesic mechanistic pathways (104). A notable 40% drop-out rate was seen using melatonin due to heavy tremor, sexual disturbances, blurred vision, and heavy-headedness (18), despite the claim that melatonin is well tolerated and safe at high doses (105). As sleep disturbances are uncommon in BMS patients, this may in part explain the poor treatment response of BMS-related pain to melatonin.

Low-level laser therapy

Photobiomodulation with low-level laser therapy (LLLT) effectively reduces chronic pain such as low back pain, temporomandibular joint disorder, and osteoarthritis (106). LLLT facilitate analgesia via its anti-inflammatory effects by increasing the secretion of serotonin, endorphins and adenosine triphosphate, augmentation of the cell membrane potential and suppressing impulse conduction velocity (107). The infrared laser has a longer wavelength compared to the red laser. It will penetrate tissue deeper, reaching the nerve fibres (108). This is observed in Spanemberg et al., 2015 where the infrared laser has an higher and significant difference in the reduction of pain score than placebo, but the red laser showed no difference with control group (34). Increasing the intensity of the laser therapy application has remarkably augmented the significance of pain score improve compared to placebo as seen is IRW3 with three sessions per week than IRW1 with one session in a week. In summary, LLLT seems to be able to contribute to BMS patients pain relief and the possibility to be used along with pharmacological and psychological treatment for a better outcome. The beneficial effect of LLT is sustained from one to four month after application of 10 sessions of LLLT (36). It is suitable to be used in medically compromised or patients on polymedication for pain as it is a non - invasive technique with no known reported adverse effects,

Saliva substitute - Biotene and Urea

BMS patients often complain of dry mouth discomfort (109). The lower salivary flow rate and thicker saliva froth may disturb the taste function (110). Urea and lysozyme lactoperoxidase (Biotene) are topical anti-xerostomic medication (saliva replacement). De Silva et al., 2014 studied urea as an adjunct therapy in BMS patients who were concurrently treated with amitriptyline (32). Amitriptyline is the first line of drug used in treating chronic neuropathic pain (111) and is known to cause dry mouth. There was no beneficial improvement seen in burning pain, taste and somatosensory despite increased oral cavity moisture and lubrication with urea or Biotene. BMS patients have decreased

unstimulated salivary flow rate but not stimulated saliva. There was no objective hyposalivation observed, which explain the lack of oral cavity lubricants efficacy in reducing the pain intensity (110,112) and the possibility of central neuropathy as the pathogenesis. Caution should be taken on the small participants size of less than 20 in both studies (32,33).

Anecdotal patient claims that regular sips of ice water help elevate the pain, which may be due to stimulation of transient receptor potential melastatin 8 (TRPM8) cold receptors or antagonist effect on TRPV1 found in the oral mucosa. The role of TRPM8 in pain analgesia has been widely contradictory debated, which may depend on its anatomical site and degree of activation (113).

Transcranial magnetic stimulation (rTMS)

Neuroimaging studies have demonstrated BMS patients to have similar brain pain matrix changes with increased functional connectivity and reduced grey matter volume as seen in other chronic pain imaging studies, indicating dysfunction of pain regulation at the CNS level (51,114). It has been established that unilateral stimulation of primary motor cortex (M1) and dorsal lateral prefrontal cortex (DLPFC) with rTMS generates a diffuse analgesic effect in both experimental and clinical pain studies (115,116). The extend rTMS induced analgesic effects depend on the stimulation patterns as the frequency and magnitudes and coil position. A single stimulation session could provide several days of analgesia, and this effect is reinforced with echoing rTMS sessions (116). This was demonstrated in Umezaki et al., 2016 with a rapid decrease in VAS scores at day 8 and 15 of rTMS treatment and a stable pain reduction score for two months (35). However, a peculiar finding on the temporary increase of pain score on day 30 and followed by a reduction in pain score on day 60 was explained by the author as possible psycho-pathophysiological disease differences (perception of pain and duration of diseases) of each patient. Further statistical analysis shows a lack of significant improvement in the mean pain score difference of short-term rTMS used (35).

rTMS is a non-invasive neuromodulation technique that could be a novel treatment in chronic pain either solely or as a complement to medication and could be useful in refractory cases. However, standardisation of therapy protocol should be established in experimental animal models before its clinical implication.

Oral appliance (Tongue protector)

A tongue protector has shown to reduce discomfort and improve oral health and quality of life (38). BMS often presented in the anterior two-thirds of the tongue, dorsal and lateral surfaces of the tongue, anterior hard palate, lip mucosa and gingiva (4). It was thought that parafunctional habits such as tongue thrust or continuous habitual rubbing over the teeth or denture and lip, cheek, or tongue biting contribute to BMS pain (117), but this contradicts the definition of BMS (1). It is hypothesised that chronic hyperactivity of trigeminal nociceptive pathways will produce intense pain response and occurrence or burning mouth feeling. The use of a tongue protector may avoid other triggering factors such as dietary stimulant (hot and spicy food, citrus food) or accidental tongue irritation on the pain site. It may create a self-false psychology security belief that the appliance protects the tongue.

Cognitive therapy

Bergdahl et al., 1995 reported an impressive reduction of three units of pain scores for both short and long-term assessment (37). The study has clearly defined its BMS patients as similar to the current ICOP recommendation (1), despite being an early year's study and proven CBT's benefits (37). BMS has frequently been associated with psychological disorders such as depression, anxiety, hypochondriasis and cancerphobia (4). It remains unclear whether anxiety and depression precede BMS or if they are a consequence of chronic pain. Treatment-resistant patients may have a contributing psychological factor. Cognitive behavioural therapy (CBT) is a common psychotherapeutic intervention for patients with chronic pain, and its effectiveness is influenced by the level of empathy received by the patient. Interestingly, females have commonly better outcomes than males. CBT

improves the patient's quality of life by allowing them to perform their daily activities without limitation and diverts their concentration on the pain, changing the thought and coping adaptive behaviours (118,119). A combination of psychopharmacological treatment may help the patient avoid the possibility of drug abuse and adverse effects. However, a larger sample size should be obtained to establish CBT benefit and to rule out the attention placebo effect as the patient was reviewed more frequently.

The authors have observed an increased awareness of acupuncture as an adjunct therapy to pharmacology treatment for BMS patients due to its encouraging analgesic results on significant VAS score reduction within the first two months of therapy (120-125). Long-term follow-up between 18 to 24 months after the initial acupuncture treatment has retained its reduction level of burning sensation and improved quality of life (122, 125). Scardina GA et al., 2010 has commented that acupuncture increase BMS patients' lip microcirculation and this will reduce the localised collection of inflammatory mediators and hence some respite from the burning pain (125). Disappointingly, acupuncture was not included in this review as the studies are either a non-randomised clinical trial on a cohort of consecutive BMS patients, lack of control group, or follow up less than two months. A further detailed study on the potential of acupuncture as a complementary therapy to reduce medications loading and increase patient compliance with medications is warranted.

In summary, the statistical analysis on the RCTs comparing intervention with placebo suggests a strong favourable outcome (SMD >1.000) for cognitive behavioural therapy, capsaicin, topical clonazepam, and laser therapy (highest to lowest) in both short- and long-term assessment. There was some evidence on the use of phytomedicines such as umPEA, herbal catuama and hypericum perforatume in short term pain score reduction. There were negligible changes in short term pain improvement in both trazodone and ALA (pooled effects) studies. However, the positive effects of ALA increase in long term assessment. Although the pooled effect of ALA pain score improvement is low, the number of

patients responding to ALA and its combination with gabapentin or vitamin were high in both short- and long-term assessments. Capsaicin, topical clonazepam and saliva substitute lysozyme lactoperoxidase showed consistent treatment effectiveness or improvement in pain comparing with placebo in both short- and long-term analysis.

Limitations

There was a substantial amount of heterogeneity in the therapeutic intervention types and method of delivery. None of the included studies has a high-grade quality of evidence in both short- and long-term outcome assessment. Short-term changes in pain score, quality of life, and adverse therapy effects may not reflect the clinical practice's real implication. Long-term outcomes data availability was minimal, with only reports on cognitive therapy, ALA, capsaicin, umPEA, topical clonazepam, and low-level laser therapy. There were other trials with similar or other treatments reported in this review but were not included mainly due to its short-term assessment of as little as two weeks (46,68). Publication limitation and error in the statistical study data led to limited statistical analysis comparing treatment and placebo groups. The significant efficacy of psychology and LLLT studies should be interpreted with caution due to unreported adverse effects (34,36,37). Varoni et al., 2018 is a cross over trial assuming a sufficient wash over period of melatonin four weeks before the next intervention (Varoni EM, 2018). The small study samples of each group (ranged 10 to 33) do not provide a robust statistical power in their results. The definition of improvement or reduction in pain for categorical data analyses (RRs) were varied across the studies as some studies may have meant almost or complete recovery while other may have meant a range of numerical decrease in VAS scores.

<u>**Conclusion**</u>

In perspective, multicentre trials are suggested to investigate various therapeutic techniques in regulating BMS pain and increase participants' number to conclude the treatment guidelines for BMS. The sustainability of pain reduction or remission is not adequately studied due to less than a year's

short assessment period. No treatment achieves a 50% pain remission in BMS. Investigating the influence of BMS biopsychosocial and neurophysiological mechanisms will provide a robust framework in integrating its various confounding aetiology factors. Studies should be ideally designed with multi-arm comparison on various pharmacological and non-pharmacological treatments to grade the treatment efficacy based on the universal accepted BMS diseases diagnosis criteria. Likewise, a greater volume on sample size, multicentre studies, and longitudinal follow-up studies will enhanced BMS treatment strategies' value. The exhibiting beneficial effects on neuroprotective and analgesic form auxiliary therapies such as phytomedicine and rTMS, and behavioural therapies CBT could be valuable alternatives or applied in conjunction with synthetic systemic drugs, with a lesser risk of adverse drugs effects and tailoring individual patient holistic treatment, rather than the disease itself.

Article Highlights

- To review systematically the evidence base medicines in treating BMS based on the recent ICOP definition.
- This review RCTs with a minimum follow up of two months, which had not been conducted by any previous systematic review.
- There is evidence on the benefit of topical oral clonazepam and capsaicin and alternative medicines such as neuroprotective agents and cognitive behavioural therapy.
- There is still insufficient long term follow up on the sustainable benefits of each treatments and its side effects.

Declaration of conflicting interests

Huann Lan Tan, Jared G. Smith and Tara Renton declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article. Jan Hoffmann is consulting for and/or serves on advisory boards of AdCel Biopharma, Allergan, Autonomic Technologies Inc., Cannovex BV, Chordate Medical AB, Eli Lilly, Hormosan Pharma, Lundbeck, Novartis, Sanofi and Teva. He has received honoraria for speaking from Allergan, Autonomic Technologies Inc., Chordate Medical AB, Lundbeck, Novartis and Teva. He received personal fees for Medico-Legal Work as well as from Oxford University Press, Quintessence Publishing, Sage Publishing and

ORCID:

Jared G. Smith: 0000-0001-6138-136X

Jan Hoffmann: 0000-0002-2103-9081

Tara Renton: 0000-0003-2331-4005

References

1. International Classification of Orofacial Pain, 1st edition (ICOP). *Cephalalgia* 2020; 40(2): 129-221.

2. Kohorst JJ, Bruce AJ, Torgerson RR, et al. The prevalence of burning mouth syndrome: a population-based study. *Br J Dermatol* 2015; 172(6): 1654-1656.

3. Bergdahl M and Bergdahl J. Burning mouth syndrome: Prevalence and associated factors. *J Oral Pathol Med* 1999; 28(8): 350-354.

4. Scala A, Checchi L, Montevecchi M, et al. Update on burning mouth syndrome: Overview and patient management. *Crit Rev Oral Biol Med* 2003; 14(4): 275-291.

5. Forssell H, Teerijoki-Oksa T, Kotiranta U, et al. Pain and pain behavior in burning mouth syndrome: A pain diary study. *J Orofac Pain* 2012; 26(2): 117-125.

6. Schiavone V, Adamo D, Ventrella G, et al. Anxiety, depression, and pain in burning mouth syndrome: First chicken or egg? *Headache* 2012; 52(6): 1019-1025.

7. Jääskeläinen SK and Woda A. Burning mouth syndrome. *Cephalalgia* 2017; 37(7): 627-647.

8. Sardella A, Lodi G, Demarosi F, et al. Burning mouth syndrome: A retrospective study investigating spontaneous remission and response to treatments. *Oral Dis* 2006; 12(2): 152-155.

9. Liu YF, Kim Y, Yoo T, et al. Burning mouth syndrome: A systematic review of treatments. *Oral Dis* 2018; 24(3): 325-334.

10. De Souza IF, Mármora BC, Rados PV, et al. Treatment modalities for burning mouth syndrome: A systematic review. *Clin Oral Investig* 2018; 22(5): 1893-1905.

11. McMillan R, Forssell H, Buchanan JA, et al. Interventions for treating burning mouth syndrome. *Cochrane Database Syst Rev* 2016; 11(11): CD002779.

12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6(7): e1000097.

13. Higgins JP, Altman DG, Gøtzsche PC, et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.

14. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 2009; 64(5): 669-677.

15. Altman DG and Dore CJ. Randomisation and baseline comparisons in clinical trials. *Lancet* 1990; 335(8682): 149-153.

16. Pagano M and Gauvreau K. Principles of biostatistics. 2nd ed. Belmont, CA: Brooks/Cole, 2000.

17. Deeks JJ and Higgins JPT. Statistical algorithms in Review Manager 5 2010, https://training.cochrane.org/handbook/statistical-methods-revman5 (2010, accessed 3 January 2021).

18. Varoni EM, Lo Faro AF, Lodi G, et al. Melatonin treatment in patients with burning mouth syndrome: A triple-blind, placebo-controlled, crossover randomized clinical trial. *J Oral Facial Pain Headache* 2018; 32(2): 178-188.

19. De Rivera Campillo ER, López-López J and Chimenos-Küstner E. Response to topical clonazepam in patients with burning mouth syndrome: A clinical study. *Bull Group Int Rech Sci Stomatol Odontol* 2010; 49(1): 19-29.

20. Heckmann SM, Kirchner E, Grushka M, et al. A double-blind study on clonazepam in patients with burning mouth syndrome. *Laryngoscope* 2012; 122(4): 813-816.

21. Tammiala-Salonen T and Forssell H. Trazodone in burning mouth pain: A placebo-controlled, double-blind study. *J Orofac Pain* 1999; 13(2): 83-88.

22. Femiano F and Scully C. Burning mouth syndrome (BMS): Double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. *J Oral Pathol Med* 2002; 31(5): 267-269.

23. Carbone M, Pentenero M, Carrozzo M, et al. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: A double-blind, randomized, placebo-controlled study. *Eur J Pain* 2009; 13(5): 492-496.

24. López-Jornet P, Camacho-Alonso F and Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: A randomized, placebo-treatment study. *J Oral Rehabil* 2009; 36(1): 52-57.

25. López-D'alessandro E and Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of Burning Mouth Syndrome: A randomized, double-blind, placebo controlled trial. *Med Oral Patol Oral Cir Bucal* 2011; 16(5): e635-640.

26. Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, et al. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. *Med Oral Patol Oral Cir Bucal* 2015; 20(4): e435-440.

27. Cano-Carrillo P, Pons-Fuster A and López-Jornet P. Efficacy of lycopene-enriched virgin olive oil for treating burning mouth syndrome: A double-blind randomised. *J Oral Rehabil* 2014; 41(4): 296-305.

28. Sardella A, Lodi G, Demarosi F, et al. Hypericum perforatum extract in burning mouth syndrome: A randomized placebo-controlled study. *J Oral Pathol Med* 2008; 37(7): 395-401.

29. Spanemberg JC, Cherubini K, De Figueiredo MA, et al. Effect of an herbal compound for treatment of burning mouth syndrome: Randomized, controlled, double-blind clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; 113(3): 373-377.

30. Pakfetrat A, Talebi M, Dalirsani Z, et al. Evaluation of the effectiveness of crocin isolated from saffron in treatment of burning mouth syndrome: A randomized controlled trial. *Avicenna J Phytomed* 2019; 9(6): 505-516.

31. Ottaviani G, Rupel K, Gobbo M, et al. Efficacy of ultramicronized palmitoylethanolamide in burning mouth syndrome-affected patients: A preliminary randomized double-blind controlled trial. *Clin Oral Investig* 2019; 23(6): 2743-2750.

32. De Silva LA, Siqueira JT, Teixeira MJ, et al. The role of xerostomia in burning mouth syndrome: A case-control study. *Arq Neuropsiquiatr* 2014; 72(2): 91-98.

33. Marino R, Torretta S, Capaccio P, et al. Different therapeutic strategies for burning mouth syndrome: preliminary data. *J Oral Pathol Med* 2010; 39(8): 611-616.

34. Spanemberg JC, López López J, De Figueiredo MA, et al. Efficacy of low-level laser therapy for the treatment of burning mouth syndrome: A randomized, controlled trial. *J Biomed Opt* 2015; 20(9): 098001.

35. Umezaki Y, Badran BW, DeVries WH, et al. The efficacy of daily prefrontal repetitive transcranial magnetic stimulation (rTMS) for burning mouth syndrome (BMS): A randomized controlled single-blind study. *Brain Stimul* 2016; 9(2): 234-242.

36. De Pedro M, López-Pintor RM, Casañas E, et al. Effects of photobiomodulation with low-level laser therapy in burning mouth syndrome: A randomized clinical trial. *Oral Dis* 2020; 26(8): 1764-1776.

37. Bergdahl J, Anneroth G and Perris H. Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: A controlled study. *J Oral Pathol Med* 1995; 24(5): 213-215.

38. López-Jornet P, Camacho-Alonso F and Andujar-Mateos P. A prospective, randomized study on the efficacy of tongue protector in patients with burning mouth syndrome. *Oral Dis* 2011; 17(3): 277-282.

39. Cinar, Levent & Kartal, Demet & Pergel, et al. Effectiveness and safety of clonazepam, pregabalin, and alpha lipoic acid for the treatment of burning mouth syndrome. *Erciyes Medical Journal* 2018; 40: 35-38.

40. Imamura Y, Shinozaki T, Okada-Ogawa A, et al. An updated review on pathophysiology and management of burning mouth syndrome with endocrinological, psychological and neuropathic perspectives. *J Oral Rehabil* 2019; 46(6): 574-587.

41. Galli F, Lodi G, Sardella A, et al. Role of psychological factors in burning mouth syndrome: A systematic review and meta-analysis. *Cephalalgia* 2017; 37(3): 265-277.

42. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. *Clin Neurophysiol* 2012; 123(1): 71-77.

43. Kim JY, Kim YS, Ko I, et al. Association between burning mouth syndrome and the development of depression, anxiety, dementia, and parkinson disease. *JAMA Otolaryngol Head Neck Surg* 2020; 146(6): 561-569.

44. Griffin CE 3rd, Kaye AM, Bueno FR, et al. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J* 2013; 13(2): 214-223.

45. Bartoshuk LM, Snyder DJ, Grushka M, et al. Taste damage: Previously unsuspected consequences. *Chem Senses* 2005; 30: i218-219.

46. Gremeau-Richard C, Woda A, Navez ML, et al. Topical clonazepam in stomatodynia: A randomised placebo-controlled study. *Pain* 2004; 108(1-2): 51-57.

47. Fenelon M, Quinque E, Arrive E, et al. Pain-relieving effects of clonazepam and amitriptyline in burning mouth syndrome: A retrospective study. *Int J Oral Maxillofac Surg* 2017; 46(11): 1505-1511.

48. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017; 6(6): CD007938.

49. Takasusuki T and Yaksh TL. The effects of intrathecal and systemic gabapentin on spinal substance P release. *Anesth Analg* 2011; 112(4): 971-976.

50. Quintero JE, Dooley DJ, Pomerleau F, et al. Amperometric measurement of glutamate release modulation by gabapentin and pregabalin in rat neocortical slices: Role of voltage-sensitive Ca2+ α2δ-1 subunit. *J Pharmacol Exp Ther* 2011; 338(1): 240-245.

51. Khan SA, Keaser ML, Meiller TF, et al. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. *Pain* 2014; 155(8): 1472-1480.

52. Yang G, Su S, Jie H, et al. Somatosensory profiling of patients with burning mouth syndrome and correlations with psychologic factors. *J Oral Facial Pain Headache* 2019; 33(3): 278-286.

53. Zorumski CF, Paul SM, Covey DF, et al. Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond. *Neurobiol Stress* 2019; 11: 100196.

54. Morillas-Arques P, Rodriguez-Lopez CM, Molina-Barea R, et al. Trazodone for the treatment of fibromyalgia: An open-label, 12-week study. *BMC Musculoskelet Disord* 2010; 11: 204.

55. Patetsos E and Horjales-Araujo E. Treating chronic pain with SSRIs: What do we know? *Pain Res Manag* 2016; 2016: 2020915.

56. Dharmshaktu P, Tayal V and Kalra BS. Efficacy of antidepressants as analgesics: A review. *J Clin Pharmacol* 2012; 52(1): 6-17.

57. Organization, World Health. WHO global report on traditional and complementary medicine. Geneva. 2019.

58. Khan H. Brilliant future of phytomedicines in the light of latest technological developments. *J Phytopharmacol* 2015; 4(1): 58-60.

59. Pan YZ and Pan HL. Primary afferent stimulation differentially potentiates excitatory and inhibitory inputs to spinal lamina II outer and inner neurons. *J Neurophysiol* 2004; 91(6): 2413-2421.

60. Yilmaz Z, Renton T, Yiangou Y, et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: Increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. *J Clin Neurosci* 2007; 14(9): 864-871.

61. Gamse R, Petsche U, Lembeck F, et al. Capsaicin applied to peripheral nerve inhibits axoplasmic transport of substance P and somatostatin. *Brain Res* 1982; 239(2): 447-462.

62. Anand P and Bley K. Topical capsaicin for pain management: Therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011; 107(4): 490-502.

63. Nolano M, Simone DA, Wendelschafer-Crabb G, et al. Topical capsaicin in humans: Parallel loss of epidermal nerve fibers and pain sensation. *Pain* 1999; 81(1-2): 135-145.

64. Derry S, Rice AS, Cole P, et al. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017; 1: CD007393.

65. Maihofner C and Heskamp ML. Prospective, non-interventional study on the tolerability and analgesic effectiveness over 12 weeks after a single application of capsaicin 8% cutaneous patch in 1044 patients with peripheral neuropathic pain: First results of the QUEPP study. *Curr Med Res Opin* 2013; 29(6): 673-683.

66. Mou J, Paillard F, Turnbull B, et al. Efficacy of Qutenza® (capsaicin) 8% patch for neuropathic pain: a meta-analysis of the Qutenza Clinical Trials Database. *Pain* 2013; 154(9): 1632-1639.

67. Altman RD and Barthel HR. Topical therapies for osteoarthritis. *Drugs* 2011; 71(10): 1259-1279.

68. Petruzzi M, Lauritano D, De Benedittis M, et al. Systemic capsaicin for burning mouth syndrome: Short-term results of a pilot study. *J Oral Pathol Med* 2004; 33(2): 111-114.

69. Jensen TS, Høye K, Fricová J, et al. Tolerability of the capsaicin 8% patch following pretreatment with lidocaine or tramadol in patients with peripheral neuropathic pain: A multicentre, randomized, assessor-blinded study. *Eur J Pain* 2014; 18(9): 1240-1247.

70. Skaper SD. Impact of inflammation on the blood-neural barrier and blood-nerve interface: From review to therapeutic preview. *Int. Rev. Neurobiol* 2017; 137: 29-45.

71. Scuderi C, Bronzuoli MR, Facchinetti R, et al. Ultramicronized palmitoylethanolamide rescues learning and memory impairments in a triple transgenic mouse model of Alzheimer's disease by exerting anti-inflammatory and neuroprotective effects. *Transl Psychiatry* 2018; 8(1): 32.

72. Passavanti MB, Fiore M, Sansone P, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: A pilot study comparing prospective and retrospective observational arms. *BMC Anesthesiol* 2017; 17(1): 171.

73. Artukoglu BB, Beyer C, Zuloff-Shani A, et al. Efficacy of Palmitoylethanolamide for pain: A meta-analysis. *Pain Physician* 2017; 20(5): 353-362.

74. Paladini A, Fusco M, Cenacchi T, et al. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: A pooled data meta-analysis. *Pain Physician* 2016; 19(2): 11-24.

75. Cocito D, Peci E, Ciaramitaro P, et al. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. *Pain Res Treat* 2014; 2014: 854560.

76. Quintão NL, Ferreira J, Beirith A, et al. Evaluation of the effects of the herbal product Catuama in inflammatory and neuropathic models of nociception in rats. *Phytomedicine* 2008; 15(4): 245-252.

77. Coppock RW and Dziwenka M. Chapter 45- St. John's Wort. In: Gupta RC (ed) Nutraceuticals Academic Press, 2016, pp.619-631.

78. Müller WE, Rolli M, Schäfer C, Hafner U. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry* 1997; 30 (Suppl 2): 102-107.

79. McCarson KE, Enna SJ. GABA pharmacology: The search for analgesics. *Neurochem Res* 2014; 39(10): 1948-1963.

80. Hippius H. St John's Wort (Hypericum perforatum): A herbal antidepressant. *Curr Med Res Opin* 1998; 14(3): 171-184.

81. Ng QX, Venkatanarayanan N andHo CY. Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. *J Affect Disord* 2017; 210: 211-221.

82. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002; 54(4): 349-356.

83. National Center for Complementary and Integrative Health. St. John's Wort and Depression: In Depth, 2017. https://www.nccih.nih.gov/health/st-johns-wort-and-depression-in-depth (2017, accessed 6 June 2021)

84. Farkhondeh T, Samarghandian S, Shaterzadeh Yazdi H, et al. The protective effects of crocin in the management of neurodegenerative diseases: A review. *Am J Neurodegener Dis* 2018; 7(1): 1-10.

85. Yorgun MA, Rashid K, Aslanidis A, et al. Crocin, a plant-derived carotenoid, modulates microglial reactivity. *Biochem Biophys Rep* 2017; 12: 245-250.

86. Li Q and Barres BA. Microglia and macrophages in brain homeostasis and disease. *Nat Rev Immunol* 2018; 18(4): 225-242.

87. Simpson DSA and Oliver PL. ROS generation in microglia: Understanding oxidative stress and inflammation in neurodegenerative disease. *Antioxidants (Basel)* 2020; 9(8): 743.

88. Singh A, Kukreti R, Saso L, et al. Oxidative stress: A key modulator in neurodegenerative diseases. *Molecules* 2019; 24(8): 1583.

89. Clifford TJ, Warsi MJ, Burnett CA, et al. Burning mouth in Parkinson's disease sufferers. *Gerodontology* 1998; 15(2): 73-78.

90. Kim JY, Kim YS, Ko I, et al. Association between burning mouth syndrome and the development of depression, anxiety, dementia, and parkinson disease. *JAMA Otolaryngol Head Neck Surg* 2020; 146(6): 561-569.

91. Cobley JN, Fiorello ML and Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. *Redox Biol* 2018; 15: 490-503.

92. Gaforio JJ, Visioli F, Alarcón-de-la-Lastra C, et al. Virgin olive oil and health: Summary of the III international conference on virgin olive oil and health consensus report. *JAEN (Spain)* 2018. Nutrients 2019; 11(9): 2039.

93. Gupta S, Jawanda MK, Arora V, et al. Role of lycopene in preventing oral diseases as a nonsurgical aid of treatment. *Int J Prev Med* 2015; 6: 70.

94. Garrido M, González-Flores D, Marchena AM, et al. A lycopene-enriched virgin olive oil enhances antioxidant status in humans. *J Sci Food Agric* 2013; 93(8): 1820-1826.

95. Ametov AS, Barinov A, Dyck PJ, et al. SYDNEY trial study group. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: The SYDNEY trial. *Diabetes Care* 2003; 26(3): 770-776.

96. Ziegler D, Low PA, Litchy WJ, et al. Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: The NATHAN 1 trial. *Diabetes Care* 2011; 34(9): 2054-2060.

97. Keith DJ, Butler JA, Bemer B, et al. Age and gender dependent bioavailability of R- and R,S-α-lipoic acid: a pilot study. *Pharmacol Res* 2012; 66(3): 199-206.

98. Vaughan R, Galley H and Kanakarajan S. Assessment of sleep in patients with chronic pain. *BJA* 2018; 120(5): E10.

99. Wilhelmsen M, Amirian I, Reiter RJ, et al. Analgesic effects of melatonin: A review of current evidence from experimental and clinical studies. *J Pineal Res* 2011; 51(3): 270-277.

100. Hussain SA, Al-Khalifa II, Jasim NA, et al. Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res* 2011; 50(3): 267-271.

101. Vidor LP, Torres IL, De Souza ICC, et al. Analgesic and sedative effects of melatonin in temporomandibular disorders: A double-blind, randomized, parallel-group, placebo-controlled study. *J Pain Symptom Manage* 2013; 46(3): 422-432.

102. Ulugol A, Dokmeci D, Guray G, et al. Antihyperalgesic, but not antiallodynic, effect of melatonin in nerve-injured neuropathic mice: Possible involvements of the L-arginine-NO pathway and opioid system. *Life Sci* 2006; 78(14): 1592-1597.

103. Ambriz-Tututi M and Granados-Soto V. Oral and spinal melatonin reduces tactile allodynia in rats via activation of MT2 and opioid receptors. *Pain* 2007; 132(3): 273-280.

104. Zhu C, Xu Y, Duan Y, et al. Exogenous melatonin in the treatment of pain: A systematic review and meta-analysis. *Oncotarget* 2017; 8(59): 100582-100592.

105. Danilov A and Kurganova J. Melatonin in Chronic Pain Syndromes. *Pain Ther* 2016; 5(1): 1-17.

106. Bjordal JM, Couppé C, Chow RT, et al. A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. *Aust J Physiother* 2003; 49(2): 107-116.

107. Pandeshwar P, Roa MD, Das R, et al. Photobiomodulation in oral medicine: A review. *J Investig Clin Dent* 2016; 7(2): 114-126.

108. Prockt AP, Takahashi A and Pagnoncelli RM. Use of low intensity laser therapy in maxillofacial surgery. *Rev Port Estomatol Cir Maxilofac* 2008; 49(4): 247-255.

109. Nasri-Heir C, Zagury JG, Thomas D et al. Burning mouth syndrome: Current concepts. *J Indian Prosthodont Soc* 2015; 15(4): 300-307.

110. Imura H, Shimada M, Yamazaki Y et al. Characteristic changes of saliva and taste in burning mouth syndrome patients. *J Oral Pathol Med* 2016; 45(3): 231-236.

111. Moore RA, Derry S, Aldington D et al. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev* 2015; 7: CD008242.

112. Lee YC, Hong IK, Na SY, et al. Evaluation of salivary function in patients with burning mouth syndrome. *Oral Dis* 2015; 21(3): 308-313.

113. Fernandez-Pena C and Viana F. Targeting TRPM8 for pain relief. *The Open Pain Journal* 2013; 6: 154-164.

114. Tan Y, Wu X, Chen J et al. Structural and functional connectivity between the amygdala and orbital frontal cortex in burning mouth syndrome: An fMRI study. *Front Psychol* 2019; 10: 1700.

115. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain* 2007; 130(10): 2661-2670.

116. Moisset X, De Andrade DC and Bouhassira D. From pulses to pain relief: An update on the mechanisms of rTMS-induced analgesic effects. *Eur J Pain* 2016; 20(5): 689-700.

117. López-Jornet P, Camacho-Alonso F and Leon-Espinosa S. Burning mouth syndrome, oral parafunctions, and psychological profile in a longitudinal case study. *J Eur Acad Dermatol Venereol* 2009; 23(3): 363-365.

118. Lim JA, Choi SH, Lee WJ, et al. Cognitive-behavioral therapy for patients with chronic pain: Implications of gender differences in empathy. *Medicine (Baltimore)* 2018; 97(23): e10867.

119. Hofmann SG, Asnaani A, Vonk IJ, et al. The efficacy of cognitive behavioral therapy: A review of meta-analyses. *Cognit Ther Res* 2012; 36(5): 427-440.

120. Sardella A, Lodi G, Tarozzi M, et al. Acupuncture and burning mouth syndrome: A pilot study. *Pain Pract* 2013; 13(8): 627-632.

121. Jurisic Kveisic A, Zavoreo I, Basic Kes V, et al. The effectiveness of acupuncture versus clonazepam in patients with burning mouth syndrome. *Acupunct Med* 2015; 33(4): 289-292.

122. Franco FR, Castro LA, Borsatto MC, et al. Combined acupuncture and auriculotherapy in burning mouth syndrome treatment: a preliminary single-arm clinical trial. *J Altern Complement Med* 2017; 23(2): 126-134.

123. Iris Z, Miroslav S, Vanja VB, et al. Efficacy of acupuncture and vitamin C in burning mouth syndrome: A pilot study. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2017; 8(1): 26-30.

124. Diep CP, Goddard G, Mauro G. Acupuncture improves pain and rest in burning mouth syndrome patients: A clinical cases. *Dental Cadmos* 2019; 87.

125. Scardina GA, Ruggieri A, Provenzana F, Messina P. Burning mouth syndrome: is acupuncture a therapeutic possibility? *Br Dent J* 2010; 209(10;E2).