RACHEL ALVARENGA BRANT DE MATTOS PEREIRA

EFICÁCIA DE DIFERENTES TRATAMENTOS PARA A SÍNDROME DA ARDÊNCIA BUCAL: *REVISÃO SISTEMÁTICA E METANÁLISE EM REDE*

Faculdade de Odontologia
Universidade Federal de Minas Gerais
Belo Horizonte
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Rachel Alvarenga Brant de Mattos Pereira

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Mestre em Odontologia.
Área de Concentração: Estomatologia

Orientador: Profª. Drª. Carolina de Castro Martins
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EFICÁCIA DE DIFERENTES TRATAMENTOS PARA A SÍNDROME DA ARDÊNCIA BUCAL: REVISÃO SISTEMÁTICA E METANÁLISE EM REDE

RACHEL ALVARENGA BRANT DE MATTOS PEREIRA

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em ODONTOLOGIA, como requisito para obtenção do grau de Mestre em ODONTOLOGIA, área de concentração ESTOMATOLOGIA.

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“Recria tua vida, sempre, sempre. Remove pedras e planta roseiras e faz doces. Recomeça.”

Cora Coralina

RESUMO

O objetivo desta revisão sistemática de ensaios clínicos randomizados (ECRs) foi avaliar a eficácia dos tratamentos para o alívio da dor da síndrome da ardência bucal (SAB). Cinco bases de dados e literatura cinzenta foram pesquisadas e as listas de referências dos estudos incluídos foram pesquisadas manualmente. Revisores independentes selecionaram estudos, extraíram dados e avaliaram o risco de viés através da ferramenta Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0). O principal desfecho foi o alívio da dor. Os desfechos secundários foram efeitos adversos, qualidade de vida, fluxo salivar, níveis de TNF-α e interleucina (IL-6), quando relatados por estudos. Para a meta análise em rede (*network meta-analysis* - NMA), foram agrupadas quatro intervenções comparáveis em diferentes geometrias para garantir o pressuposto da transitividade: terapia de fotobiomodulação (PBMT), ácido alfa-lipóico (ALA), fitoterápicos e ansiolíticos/antidepressivos. As estimativas de efeitos para dor foram: diferença de média (DM) para desfechos contínuos pois os estudos usaram escalas comparáveis variando de 0 a 10 para dor; e risco relativo (RR) para desfechos binários. Para qualidade de vida, a diferença de média padronizada (DMP) foi calculada pois os estudos usaram escalas diferentes. Para calcular a DM, usou-se a média e desvio padrão (DP) em baseline e no último momento de cada intervenção. Para ambas todas as estimativas, foram calculados os correspondentes intervalos de confiança (IC) de 95%. A certeza da evidência foi avaliada usando a abordagem GRADE para NMA. Para a certeza da evidência, foi avaliado ser havia problemas de risco de viés, inconsistência, evidência indireta, viés de publicação, intransitividade, imprecisão e incoerência. Para imprecisão, foi considerada a diferença mínima importante (*minimal importante difference* - MID) necessária para tomada de decisão de tratamento comparando intervenção e placebo, sendo este último o comparador. Para dor relatada como DM, o MID foi -1 ou 1, e 0,32 ou 1,68 para RR. A classificação de Cohen foi usada para determinar um MID de grande efeito para a qualidade de vida (DMP): < -0,8 ou >0,8. Para otimizar a interpretação dos resultados da NMA e a aplicabilidade clínica, foram usadas a abordagem GRADE minimamente contextualizada para dor e o parcialmente contextualizada para qualidade de vida. O ansiolítico (clonazepam) provavelmente reduz a dor da SAB quando comparado ao placebo (DM: - 1,88; IC 95%: -2,61; -1,16, certeza moderada). A DM do fluxo salivar aumentou ligeiramente em -0,20 tanto para o ansiolítico quanto para o placebo. A DM, para os níveis de IL-6 e TNF-α, foi maior para PBMT do que placebo, o que significa uma diminuição mais pronunciada nesses níveis para PBMT. Apesar de PBMT, pregabalina e fitoterápicos apresentarem superioridade quando comparados ao placebo, a certeza da evidência foi baixa ou muito baixa. A maioria dos demais tratamentos teve baixa e muito baixa certeza, principalmente devido à imprecisão e evidência indireta. Nenhum tratamento causou impacto na qualidade de vida. Os efeitos adversos foram pouco reportados e não influenciaram o curso dos tratamentos. Mais ECRs comparando tratamentos com placebo são encorajados para confirmar a evidência. Até o momento, o melhor tratamento para SAB é o ansiolítico clonazepam. No entanto, a aplicabilidade relacionada à eficácia, efeitos adversos e qualidade de vida são limitados à 120 dias.

Palavras-chave: Metanálise. Doenças estomatognáticas. Doenças da boca. Ensaios clínicos.

ABSTRACT

This systematic review of randomized controlled trials (RCTs) aimed to assess the effectiveness of treatments for pain relief of burning mouth syndrome (BMS). Five databases and grey literature were searched, and the reference lists of included studies were hand-searched. Independent reviewers selected studies, extracted data, and assessed the risk of bias (RoB 2.0). The main outcome was pain relief. The secondary outcomes were adverse effects, quality of life, salivary flow, TNF-α and interleukin (IL-6) levels, when reported by trials. For the network meta-analysis (NMA), four comparable interventions were grouped into different geometries to ensure the transitivity assumption: photobiomodulation therapy (PBMT), alpha-lipoic acid (ALA), phytotherapics, and anxiolytics/antidepressants. The effect estimate was a mean difference (MD) for continuous outcomes instead of the standardized mean difference (SMD), as studies used comparable scales varying from 0 to 10 for pain; and risk ratio (RR) for binary outcomes. The SMD was calculated for quality of life as studies used different scales. To calculate MD, we used mean and standard deviation (SD) at the baseline and at the last time point of each intervention. For both estimates, corresponding 95% confidence intervals (CI) were calculated. The GRADE approach for NMA was used to assess the certainty of the evidence. We rated down the certainty of evidence if there were problems due to the risk of bias, inconsistency, indirectness, publication bias, intransitivity, imprecision, and incoherence. We considered the minimal important difference (MID) necessary to a treatment decision comparing intervention and placebo (comparator) to rate imprecision. For pain reported as MD, the MID was -1 or 1, and 0.32 or 1.68 for RR. The Cohen classification was used to determine a MID of large effect for the quality of life (SMD): < -0.8 or >0.8 To optimize the interpretation of results of NMA and clinical applicability, we followed the GRADE minimally contextualized framework for pain and the partially contextualized framework for quality of life. The anxiolytic (clonazepam) probably reduces pain of BMS compared to placebo (MD: - 1.88; 95% CI: -2.61; -1.16, moderate certainty). The MD of salivary flow slightly increased in -0.20 for both the anxiolytic and placebo (Heckmann et al. 2012). The MD for IL-6 and TNF-α levels was higher for PBMT than placebo, which means a more pronounced decrease in these levels for PBMT. Although PBMT, pregabalin and phytotherapics showed superiority compared to placebo, the certainty was low or very low. The majority of the other treatments had low and very low certainty, mainly due to imprecision and indirectness. No treatment improved the quality of life. Adverse effects were rarely reported and did not influence the course of treatments. More RCTs comparing treatments against placebo are encouraged to confirm the evidence. So far, the anxiolytic clonazepam is the best treatment for BMS. However, the applicability of effectiveness, adverse effects and quality of life are limited to 120 days.

Keywords: Meta-analysis. Stomatognathic diseases. Mouth diseases. Clinical trials.

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LISTA DE ABREVIATURAS E SIGLAS

ALA	Ácido Alfa-lipóico
ATP	Trifosfato de Adenosina
BMS	Burning Mouth Syndrome
CI	Confidence Interval
ECR	Ensaios Clínicos Randomizados
GABA	Gabapentina
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation Approach
Il-6	Interleucina
MD	Mean Difference
MID	Minimal Important Difference
NMA	Network Meta-analysis
PBMT	Photobiomodulation Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized Controlled Trial
RoB	Revised Cochrane Risk-of-bias Tool for Randomized Trials
RR	Risk Ratio
SAB	Síndrome da Ardência Bucal
SD	Standard Deviation
SMD	Standardized Mean Difference
SNC	Sistema Nervoso Central
TNF-α	Tumor Necrosis Factor
Um-PEA	Ultramicronized Palmitoylethanolamide
VAS	Visual Analogic Scale

SUMÁRIO

1 INTRODUÇÃO

A síndrome da ardência bucal (SAB) ou boca ardente foi descrita pela primeira vez no século XIX. Foi caracterizada por Butlin e Oppenhein no início do século XX, como uma sensação de queimação e formigamento na língua, estendendo-se muitas vezes aos tecidos adjacentes (GILPIN, 1936).

A SAB é uma desordem complexa, crônica caraterizada por sintomas como ardor, dor ou prurido da mucosa oral, sem alterações clínicas visíveis, laboratoriais ou modificações do fluxo salivar (DANHAUER *et al.,* 2002; KOMIYAMA *et al.,* 2013). A síndrome de ardência bucal é também chamada de estomatodinia ou glossidinia (quando confinada à língua) ou síndrome de ardência bucal primária (ICOP, 2020).

A síndrome da ardência bucal é caracterizada como uma sensação de queimação intraoral ou disestésica, recorrente diariamente por mais de duas horas por dia, por mais de três meses, sem lesões causadoras evidentes ao exame clínico (ICOP, 2020). A dor é contínua e de intensidade moderada a grave. Embora possa variar, muitas vezes, é de menor intensidade pela manhã e se agrava durante a noite. Raramente perturba o sono. É mais frequentemente sentida na língua, mas, também, pode ocorrer em qualquer parte da mucosa intraoral. A dor da SAB é geralmente bilateral, embora possa ocorrer, em raras ocasiões, unilateralmente e não obedeça às distribuições nervosas periféricas. Além disso, os pacientes frequentemente queixam-se de distorção do paladar (disgeusia), diminuição do paladar (hipogeusia) ou boca seca (xerostomia), apesar da salivação normal (JÄÄSKELÄINEN, 2012). As evidências sugerem que esse transtorno tenha uma causa multifatorial, em que alterações neurológicas, psicogênicas e fatores hormonais sejam alguns dos fatores que contribuam para a doença. Atualmente, a SAB é classificada como dor crônica idiopática (JÄÄSKELÄINEN 2012; SPANEMBERG *et al.a,* 2012; TAN *et al.,* 2022).

Apesar de existirem vários estudos sobre esta condição, algumas questões sobre a SAB ainda são debatidas e representam um desafio para pesquisadores e clínicos. O grande dilema deve-se ao fato desta patologia poder potencialmente surgir a partir de inúmeras fatores locais ou sistêmicos (SPANEMBERG *et al.,* 2012a). A SAB pode ser classificada em primária ou secundária. Neste modelo, a SAB primária refere-se à uma persistente sensação de queimação, na ausência de achados

clínicos, e a SAB secundária refere-se à uma sensação de queimação relacionada à uma condição subjacente identificável. A segunda delas é resultante de condições patológicas locais e sistêmicas e, portanto, potencialmente sensíveis à terapia direcionada à etiologia original (KLEIN *et al.,* 2020; SCALA *et al.,* 2003). O manejo de pacientes com SAB é desafiador, podendo ser frustrante para o clínico. O diagnóstico correto de SAB e a exclusão de possíveis infecções locais ou sistêmicas são fatores fundamentais para a realização de um tratamento adequado. Os mecanismos complexos da SAB precisam ser investigados para o estabelecimento de um tratamento eficaz para este transtorno. É, também, importante avaliar a qualidade de vida desses pacientes e reconhecer o impacto que esta condição tem em suas vidas, pois, os sintomas podem perdurar por muitos anos (SPANEMBERG *et al.,* 2012a).

Para o diagnóstico de SAB, a mucosa oral deve estar intacta, com todos os aspectos clínicos dentro dos padrões de normalidade. A SAB é, portanto, um diagnóstico de exclusão, feito somente após o afastamento de todas as outras causas de dor e/ou queimação intraorais (KOLKKA-PALOMAA *et al.,* 2015). O diagnóstico diferencial deve levar em consideração dores orofaciais crônicas e doenças bucais dolorosas que causam lesões na mucosa, tais como aftas, candidíase, síndrome de Sjögren, hipossalivação, entre outros. Para a conclusão do diagnóstico, outras condições sistêmicas também devem ser consideradas, como alterações hormonais, deficiências vitamínicas, uso de medicamentos e diabetes (DE SOUZA *et al.*, 2018).

A etiologia e a fisiopatologia da SAB permanecem desconhecidas. O papel dos sistemas nervosos periférico e/ou central é relatado por estudos envolvendo testes sensoriais quantitativos e métodos funcionais de imagem (KOLKKA-PALOMAA *et al.,* 2015; JÄÄSKELÄINEN 2012). As evidências sugerem que a SAB primária pode ter origem neuropática, e que, lesões em diferentes níveis do sistema nervoso periférico ou central podem estar envolvidas na sua patogênese. Três hipóteses neuropáticas distintas têm implicado na etiologia da SBA primária: neuropatia sensorial de fibras pequenas; neuropatia subclínica mandibular, lingual ou trigeminal; e hipofunção de neurônios dopaminérgicos (MOGHADAM-KIA and FAZEL, 2017).

Biópsias de língua realizadas em pacientes com SAB revelaram uma menor densidade de fibras de pequenas terminações nervosas, em comparação com controles sem a doença, consistente com uma neuropatia de pequenas fibras. Outro subconjunto de SAB pode constituir uma neuropatia subclínica trigeminal. Esta teoria é baseada em anormalidades nos reflexos massetérico e do ato de piscar, que são

comumente avaliados ao testar a função do nervo trigêmeo. A terceira hipótese neuropática para a etiologia da SAB primária implica que os pacientes apresentam a dor mediada no sistema nervoso central (SNC). Isto se deve, possivelmente, devido à hipofunção de neurônios dopaminérgicos, nos gânglios da base, que são envolvidos na modulação inibitória da dor. As alterações neste sistema (SNC) são semelhantes às observada na doença de Parkinson, e há alguma evidência de um aumento da incidência de SAB em pacientes com esta doença (JÄÄSKELÄINEN, 2012). Níveis diminuídos de dopamina, nos gânglios da base de alguns pacientes com SAB, podem representar uma via de doença comum, para SAB e depressão (KLEIN *et al.,* 2020; MOGHADAM-KIA and FAZEL, 2017).

Alguns estudos mostraram uma alta prevalência de transtornos psiquiátricos ou psicológicos como depressão, ansiedade, somatização e transtornos de personalidade em pacientes com SAB (DE SOUZA *et al.,* 2012; KIM *et al.,* 2020; SCHIAVONE *et al.,* 2012). Ainda existem controvérsias se fatores psicogênicos são eventos primários ou secundários nestes pacientes (DE SOUZA *et al.,* 2012; KLASSER *et al.,* 2016; SCHIAVONE *et al.,* 2012).

A prevalência da SAB na população geral é estimado em 2,5 a 5,1% (COCULESCU *et al.,* 2015). Nos homens, nenhum caso foi encontrado antes da faixa etária dos 40 a 49 anos. Esta, foi de 0,7%, aumentando para 3,6% em homens mais velhos. Nas mulheres, também, não foi encontrado nenhum caso na faixa etária mais jovem. A prevalência aumentou de 0,6% para 12,2%, na faixa etária de mulheres mais velhas (30 a 39 anos) (BERGDAHL and BERGDAHL, 1999). A prevalência de SAB é relatada variando amplamente de 0,7% a 15% em várias raças, populações e ambientes (BERGDAHL and BERGDAHL, 1999; COCULESCU *et al.,* 2015). Uma recente revisão reportou uma prevalência de 1,73% entre os estudos de base populacional e, nos estudos clínicos, uma prevalência de 7,72% (WU *et al.,* 2021). Outro estudo relata a prevalência dos sintomas variando de 0,7% a 4,6% (AGGARWAL and PANAT, 2012). A variação da prevalência entre os estudos, deve-se à diferentes definições e critérios utilizados no diagnóstico desta desordem. A prevalência desta condição, aumenta com a idade, em homens e mulheres, afetando principalmente o sexo feminino, entre a quinta e a sétima década de vida (TAN *et al.,* 2022).

É relatado uma grande possibildade de tratamentos para a SAB. Os resultados dos estudos analisados apresentam poucos trabalhos avaliando medidas

de qualidade de vida, o que dificulta a comparação entre os tratamentos (ZAKRZEWSKA and BUCHANAN 2016).

Atualmente, as principais modalidades de tratamento para o manejo da SAB, descritas na literatura são os ansiolíticos e antidepressivos, já que a dor e o sofrimento psíquico estão intimamente interligados. Pacientes que sofrem de dor crônica correm risco de desenvolver ansiedade e depressão em longo prazo. Da mesma forma, pacientes com transtornos de humor podem relatar dor somática (ADAMO *et al*., 2020). Os efeitos terapêuticos mais promissores foram aqueles observados com o clonazepam, com significativa redução da dor, após a aplicação tópica ou sistêmica. Entre os principais efeitos adversos com esse tipo de tratamento são febre, dor de cabeça, falta de apetite, sonolência, tontura, diarreia e mialgia. Os ansiolíticos e antidepressivos podem causar alterações fisiológicas e dependência psicológica se forem usadas de forma sistêmica ou tópica (SLEBIODA *et al.,* 2020).

Como opção de tratamento não farmacológico, surgiu a terapia fotodinâmica. Ela é utilizada devido à sua capacidade de modular os processos metabólicos, bioquímicos e fotofísicos que transformam a luz do laser em energia útil para as células. A energia provoca reações mitocondriais e aumentos na produção de trifosfato de adenosina (ATP), níveis de cálcio intracelular e número de mitoses. A radiação laser de baixa intensidade possui propriedades analgésicas, anti-inflamatórias e de reparação tecidual (FARIVAR *et al.,* 2014). Em SAB, a terapia fotodinâmica parece ter um efeito positivo apenas se usada mais frequentemente. Uma possível explicação para a ação analgésica da terapia fotodinâmica está relacionada à inibição dos mediadores da dor e ao aumento do potencial de membrana, reduzindo a velocidade de condução do impulso nervoso (DE SOUZA *et al.*, 2018).

Outra opção de tratamento encontrada na literatura são os fitoterápicos. Estes medicamentos são substâncias naturais e incluem uma grande variedade de agentes como capsaicina, catuama e camomila (JØRGENSEN and PEDERSEN 2017; SPANEMBERG *et al.,* 2012b; VALENZUELA *et al.,* 2016). Uma revisão sistemática demonstrou que os fitoterápicos catuama e enxaguante bucal de capsaicina produziram resultados positivos na melhora dos sintomas da SAB, quando comparado ao placebo. Não houve relatos de efeitos adversos no grupo dos tratamentos. Os resultados desta revisão sugerem que os fitoterápicos são potenciais

terapias para o tratamento da SAB, devendo ser fonte de estudo de novos ensaios clínicos (DE SOUZA *et al.*, 2018).

O ácido alfa-lipóico (ALA) é um outro grupo de substâncias utilizadas para o tratamento da SAB. Ele é um potente antioxidante que é produzido naturalmente no organismo. Também pode ser encontrado em alguns alimentos naturais, como batatas, tomates e espinafres. Até o momento, sua principal contribuição é abrandar o envelhecimento cutâneo, pois regenera e fortalece os efeitos de outros antioxidantes biológicos. Além disso, ele parece favorecer a produção do fator de crescimento neural e tem sido usado no tratamento da neuropatia diabética (ÇINAR *et al.,* 2018; PALACIOS-SÁNCHEZ *et al.,* 2015). Com base nesses dados, houve tentativas de demonstrar a sua eficácia no manejo da SAB e concluiu-se que o ALA parece proporcionar benefícios nesta área (PALACIOS-SÁNCHEZ *et al.,* 2015).

Outras opções de tratamento como a gabapentina (GABA) e a pregabalina, lubrificante tópico, acupuntura, cloridrato de benzidamina, estímulo eletromagnético, melatonina e terapia cognitiva são descritos na literatura, com evidências limitadas (BECKER *et al.,* 2021; ÇINAR *et al.,* 2018; JURISIC KVESIC *et al.,* 2015; LÓPEZ-D'ALESSANDRO and ESCOVICH 2011; MARINO *et al.,* 2010; SARDELLA *et al.,* 1999; UMEZAKI *et al.,* 2016; VARONI *et al.,* 2018).

Este trabalho foi desenvolvido devido às limitações dos resultados de revisões sistemáticas presentes na literatura. O tratamento da SAB é uma incógnita para clínicos e pesquisadores e, por isso, necessita-se de mais estudos comparativos. Assim, realizamos uma revisão sistemática com meta-análise em rede (*network meta-analysis - NMA*) para agrupar as possibilidades terapêuticas para ao tratamento da SAB.

Em um universo de diversas possibilidades de terapia, este trabalho buscou preencher uma lacuna na literatura, no que diz respeito à SAB e a seus tratamentos. Até hoje, na literatura, ainda não existe um Guideline para o tratamento da SAB.

Nesse sentido, o objetivo desta meta-análise de rede foi investigar a eficácia dos tratamentos para o alívio da dor associada aos sintomas da SAB, em comparação com nenhuma intervenção ou placebo.

2 OBJETIVO

2.1 Objetivo geral

Realizar uma revisão sistemática e buscar evidências científicas da eficácia de todos os tipos de tratamentos para o alívio da dor da síndrome da ardência bucal.

2.2 Objetivo específico

Avaliar os efeitos adversos, qualidade de vida, fluxo salivar, níveis de TNF-α e interleucina (IL-6), quando relatados pelos estudos.

3 METODOLOGIA

Será apresentada no formato de artigo científico intitulado:

TREATMENTS FOR BURNING MOUTH SYNDROME: A NETWORK META-ANALYSIS

4 ARTIGO

Artigo submetido e formatado de acordo com as normas do periódico Journal of Dental Research; Fator de impacto: 6.116. Qualis Odontologia: A1.

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Title: Treatments for burning mouth syndrome: a network meta-analysis

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Abstract

The aim of this systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) was to evaluate the effectiveness of treatments for pain relief of burning mouth syndrome (BMS). Five databases and grey literature were searched. Independent reviewers selected studies, extracted data, and assessed the risk of bias (RoB 2.0). The primary outcome was pain relief or burning sensation, and the secondary outcomes were side effects, quality of life, salivary flow, TNF-α and interleukin (IL-6) levels. Four comparable interventions were grouped into different network geometries to ensure the transitivity assumption for pain: photobiomodulation therapy (PBMT), alpha-lipoic acid (ALA), phytotherapics, and anxiolytics/antidepressants. Mean difference (MD) and 95%CI were calculated for continuous outcomes. The minimal important difference (MID) to consider a therapy beneficial against placebo was at least MD: -1 for relief of pain. The GRADE approach for NMA with a minimally contextualized framework and the magnitude of the effect was used to interpret the results. Forty-four trials were included (24 in the NMA). The anxiolytic (clonazepam) probably reduces pain of BMS when compared to placebo (MD: -1.88; 95% CI: -2.61; -1.16; moderate certainty). PBMT (MD: -1.90; 95% CI: -3.58; -0.21) and pregabalin (MD: -2.40; 95%CI: -3.49; -1.32) achieved the MID of beneficial effect with low or very low certainty. Among all tested treatments, only clonazepam is likely to reduce pain of BMS when compared to placebo. The majority of the other treatments had low and very low certainty, mainly due to imprecision, indirectness and intransitivity. More RCTs comparing treatments against placebo are encouraged to confirm the evidence and test other possible alternative treatments.

PROSPERO: # CRD42021255039 (Efficacy of different treatments for burning mouth syndrome: systematic review).

Introduction

Burning mouth syndrome (BMS) is an intraoral burning or dysesthesia sensation, recurring for more than 2 hours per day for more than three months, without evident causative lesions during the clinical examination. The pain is usually bilateral, but on rare occasions, it is unilateral, and the intensity fluctuates. The most common site is the tip of the tongue. In addition, there is subjective xerostomia, dysesthesia, and altered taste in two-thirds of reported cases (IHS 2013; ICOP 2020). BMS affects more women above 50 years old, with a prevalence of 1:1,000 individuals (Moghadam-Kia and Fazel 2017).

The growing evidence associating BMS with psychological comorbidities has suggested anxiolytics, antidepressants, and psychological therapies in BMS management (McMillan et al. 2016). The photobiomodulation therapy (PBMT) has emerged as a non-pharmacological treatment option, with analgesic, anti-inflammatory, and tissue repairing properties (de Souza et al. 2018). Other tested treatments include phytotherapics (natural substances including various agents such as capsaicin, catuama and chamomile) (Tan et al. 2022) and alpha-lipoic acid (ALA), which is used in patients with BMS acting as a neuroprotector and thus prevent neural damage (Spanemberg et al. 2012a). Gabapentin (GABA), pregabalin, topical lubricant, acupuncture, benzydamine hydrochloride, electromagnetic stimulus, melatonin, ultramicronized palmitoylethanolamide and cognitive therapy were also tested by clinical trials with limited and controversial evidence (Moghadam-Kia and Fazel 2017; Tan et al. 2022).

So far, there is no consensus on the best treatment for the BMS. One network meta-analysis (NMA) found that the anxiolytic clonazepam and capsaicin are promising treatments for BMS (Häggman-Henrikson et al. 2017). However, this NMA included only five studies for BMS, and the study was limited to pharmacological therapies. Therefore, it is urgent to search for evidence of the best treatment modalities against placebo or no treatment to help clinicians treat these patients. Therefore, this systematic review and network meta-analysis (NMA) aimed

to investigate the effectiveness of all treatments for the relief of pain associated with BMS compared to no intervention or placebo.

Materials and Methods

This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement for reporting NMAs (Hutton et al. 2015) and was registered *a priori* at PROSPERO database (#CRD42021255039). No changes were made necessary in the protocol after the start of the review.

Eligibility Criteria

The clinical question (PICO question) was: 'In patients with BMS, what is the efficacy of treatments for the relief of pain associated with the symptoms of BMS compared to no intervention or placebo?'

P: adults with BMS, above 18 years old, from both sexes.

I: (intervention): some treatments were decided *a priori* to be included in this review, such as: PBMT, phytoterapics, ALA, anxiolitic and antidepressive, ultramicronized palmitoylethanolamide (um-PEA), cognitive therapy, GABA, pregabalin, topical lubricant, acupuncture and others. However, any other treatment found during the search would be considered.

C: placebo or no treatment.

O: pain (also referred as "burning sensation").

We included randomized controlled trials (RCTs) with adults above 18 years old, of both sexes, diagnosed with BMS by a dentist or oral health professional using validated criteria according to the (IHS 2013; ICOP 2020); any treatment; pain measured before and after treatment. Exclusion criteria were: quasi-randomized studies, non-randomized studies, and trials without a comparison group; pregnant or lactating women, and patients with the following

pathologic alteration: lesions of the oral mucous membranes, systemic diseases such as diabetes, anemia, vitamin B1, B2, B6, B12, Fe, zinc and folic acid deficiency; gastroesophageal reflux, patients undergoing previous head and neck radiotherapy, Sjogren's disease, syndromes, allergies, candidiasis and hyposalivation due to other causes rather than BMS.

Information Sources

The following databases were searched from interception up to December 2021: MedLine (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews and Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus. Ongoing trials were searched on Clinical Trials and International Clinical Trials Registry Platform (ICTRS), and grey literature on Proquest Dissertation & Theses database. We manually searched the reference list of included studies. There were no restrictions on publication date and language. Search strategies are presented in Appendix Table 1. The retrieved studies were organized on The Endnote Software version 20.0.1 (Clarivate Analystics).

Study Selection

Paired independent reviewers (RAB, GHMP) screened studies based on titles and abstracts and later by full texts using the Rayyan online software (https://www.rayyan.ai/). Before each screening stage, the reviewers underwent two calibration and training exercises with 10% of the studies. All disagreements were solved by discussion and consensus.

Data Extraction and Risk of Bias Assessment

Paired independent reviewers (RAB, GHMP, RPEL, FVB) extracted data and assessed the risk of bias of included studies, following an extraction excel spreadsheet. Data extracted were: study location, language, sample size, age, sex, authors, type of treatment, follow-up, the clinical score used for pain, dropouts, funding, and conflict of interest. The principal investigator (PI) trained the reviewers using 10% of the included trials. Disagreements were resolved by consensus between the pair of reviewers. To avoid potential biases due to different

pairs of reviewers, the PI cross-checked all data extraction. The Cochrane Risk of Bias Tool for randomized trials (RoB 2.0) was used to assess the risk of bias in each outcome (Sterne et al. 2019). The assessment of the risk of bias followed the same method as data extraction. The PI trained the reviewers with the same 10% of trials. Disagreements were solved by a discussion with the PI. The senior author was responsible for the final vote if the discussion was not enough for a decision.

Outcomes

The primary outcome was pain relief or burning sensation, and both terminologies were named as "pain". The secondary outcomes were side effects, quality of life, salivary flow as a consequence of the treatment, TNF-α and interleukin (IL-6) levels, when reported by trials.

For pain, we considered the pain scales used by the authors. In addition, for primary and secondary outcomes, we collect sample, mean, median, standard deviation (SD), 95%CI, range (continuous variables), and the number of patients at baseline and during each follow-up time when reported.

Data synthesis and statistical methods

A frequency distribution was calculated for study characteristics using Microsoft Excel. For the NMA, we considered four comparable intervention groups to pool into different geometries for the transitivity assumption: PBMT, ALA, phytotherapics, and anxiolytics/antidepressants. It might be challenging to defend transitivity if there are differences among interventions, especially regarding the different treatment routes of the comparator (placebo) (Salanti 2012). For example, mimicking PBMT (placebo) takes a different route compared to placebo pills for oral medications. Consequently, when splitting treatments into different geometries, there were few studies per comparison, and a random effect frequentist NMA was preferred (Dias et al. 2018). Multi-arm trials with two or more similar treatments with different dosages were merged into a single arm to be included in the NMA (e.g., PBMT

with different wavelengths, ALA with different dosages, and placebo was merged with "no treatment"). Other multi-arm trials with different treatments were included in the NMA. The effect estimate was mean difference (MD) for continuous outcomes instead of the standardized mean difference (SMD), as studies used comparable scales varying from 0 to 10 for pain; and to avoid the effect of the SD on the estimate of the SMD (Daly et al. 2021). To calculate MD, we used the mean and SD at the baseline and at the last time point of each intervention. Risk ratio (RR) was used for dichotomous outcomes (pain). The 95% confidence intervals (CI) were calculated for all estimates. We used the networkplot command of Stata version 15.1 (StataCorp - USA) to draw the network plots and R version 3.4.3 (R Core Team) with the netmeta package version 1.4-0 for NMA. Direct and indirect treatment effects were calculated, assessing the comparative effectiveness of interventions. Review Manager Software version 5.4 (Review Manager, UK) was used to plot the direct comparisons. Incoherence (i.e., inconsistency in the model) was assessed by comparing direct estimates with indirect estimates and final network estimates using the back-calculation method. Incoherence in the entire network was evaluated using a design-by-treatment model with two-tailed threshold of $p \leq 0.05$ (Lu and Ades 2012). The ranking probabilities were calculated. For the NMA, the reference was the most connected intervention; and placebo as the comparator to report the paper, considering the lack of a gold standard treatment for BMS (Brignardello-Petersen et al. 2020a).

Some interventions did not connect to any network plot due to the lack of a common comparator. For this reason, we performed paired meta-analyses using Review Manager Software.

For the quality of life, a frequentist NMA was performed the same way described above. As different scales reported the quality of life, the effect estimates were calculated as SMD and 95%CI (da Costa et al. 2013). Side effects were narratively described once it was not possible to pool data together for meta-analysis. We calculated MD and 95%CI for salivary flow, IL-6

and TNF-α, from baseline to the last time point. However, we chose to describe the results narratively instead of running a meta-analysis once each comparison included a single study (Heckmann et al. 2012; Pezelj-Ribarić et al. 2013).

Interpretation of results

The certainty of the evidence was assessed for each network estimate using the Grading of Recommendations, Assessment, Development, and Evaluation approach (GRADE) for NMA. The certainty starts with high for RCTs. We rated down the certainty of evidence if there were problems due to the risk of bias, inconsistency, indirectness, publication bias, intransitivity, imprecision and incoherence. (Bonner et al. 2018; Brignardello-Petersen et al. 2018a; Puhan et al. 2014). The detailed approach is described in Appendix Flowchart 1, Appendix Table 2.

For imprecision, we considered the minimal important difference (MID) necessary to a treatment decision comparing intervention and placebo (comparator) (Brignardello-Petersen et al. 2018b; Carrasco-Labra et al. 2021). For pain reported as MD, the MID was -1 or 1, and 0.32 or 1.68 for RR (Chen et al. 2010; Dworkin et al. 2009). The Cohen classification was used to determine a MID of large effect for the quality of life (SMD): < -0.8 or >0.8 (Schünemann et al. 2021). For both MD and SMD, negative values indicate that the intervention has a beneficial effect when compared to placebo; positive values mean that the intervention has a harmful effect when compared to placebo. For RR, values <1 indicate that the intervention has a beneficial effect when compared to placebo; and values >1 indicate that the intervention has a harmful effect when compared to placebo.

To optimize the interpretation of results of NMA and clinical applicability, we followed the GRADE minimally contextualized framework for pain and the partially contextualized framework for quality of life (Brignardello-Petersen et al. 2020a; Brignardello-Petersen et al. 2020b). The judgments, classification and conclusions were based on the magnitude of the

effects and the certainty of the evidence. Summary of Findings (SoF) tables were built for each outcome.

Results

Study Selection

Forty-four RCTs were included in this review, with 24 contributing to the NMA (Figure 1). Appendix References 1 shows the list of included studies, and Appendix Table 3 shows the list of excluded studies with reasons.

Table 1 shows the studies' characteristics. Most studies were conducted in Europe (71%), published in the English language (100%), and after 2010 (70.45%). No study was industry-funded. The total number of patients was 2,283, with a mean age of 64.9 years ±3.3 years.

Risk of bias

Overall, 6.8% of studies were at low risk of bias, 61.3% had some concerns, and 31.8% were at high risk of bias (Appendix Figure 1). The studies were judged at low risk of bias regarding "randomization process" (56.8%); "deviation from intended intervention" (61.4%); "missing outcome data" (95.5%); and "measurement of the outcome" (72.7%). However, several studies had some concerns, especially "selection of the reported outcome" (90.9%) that contributed to the overall judgment as some concerns.

Pain relief for BMS

Studies Included in NMA

Table 2 and Figure 2 show the SoF table with the minimally contextualized framework and network geometries with the four groups of treatments. All except one treatment (anxiolytic) had low to very low certainty, which shows the lack of certainty regarding their efficacy. The only treatment that showed a beneficial effect compared to placebo achieving the

MID with moderate certainty was the anxiolytic (clonazepam, MD: - 1.88; 95% CI: -2.61; -1.16 – shown in bold in Table 2).

The following treatments achieved the MID, however, with low to very low certainty: PBMT (MD: -1.90; 95%CI: -3.58; -0.21); tongue protector + phytoterapic (MD: -1,37; 95%CI: -4.29; 1.55); pregabalin (MD: -3.19; 95% CI: -5.38; -1.00); phytoterapic (MD: -1.74; 95% CI: -4.02; 0.55); lubricant (MD: -1.04; 95% CI: -3.26; 1.19). Note that all above-cited 95CI%s cross the line of null effect and the MID, showing very serious imprecision (except for PBMT with serious imprecision - 95%CI crosses the MID). Antidepressants did not achieve the MID in any analysis. And ALA showed harmful effects compared to placebo for the continuous and binary outcome analysis.

The Appendix material has Geometries 1-6, Plots 1-6, Figures 2-13 and League Table 1-6 detailing all the NMA results.

Pairwise meta-analysis

It was not possible to include the following treatment to the NMA: um-PEA, cognitive therapy, GABA+pregabalin, topical lubricant, acupuncture, benzydamine, electromagnetic stimuli, melatonin, dexamethasone and lafutidine. The paired meta-analyses and the certainty of the evidence showed the uncertainty of the majority of treatments (Appendix Table 4; Appendix Forest Plots 1-12).

Narrative synthesis

Some comparisons were neither included in the meta-analysis nor the NMA, and the Appendix Box 1 shows the narrative synthesis.

Secondary outcomes

The NMA for quality of life is shown in Table 3 and Figure 2. No treatment improved the quality of life when compared to placebo, as none had a large beneficial effect with moderate or high certainty.

Appendix Table 5 shows the salivary parameters collected at baseline and last time point. The MD of salivary flow slightly increased in -0.20 for both the anxiolytic and placebo (Heckmann et al. 2012). The MD for IL-6 and TNF-α levels was higher for PBMT than placebo, which means a more pronounced decrease in these levels for PBMT (Pezelj-Ribarić et al. 2013).

Twenty-seven trials (61.36%) reported side effects for a few patients (Table 4). The majority of trials reported no serious adverse events for any treatment.

Discussion

A reasonable number of eligible treatments showed positive results, despite discrepancies and variations in the parameters of each treatment group, the limited number of included studies in each comparison, different follow-up times, and missing data. However, the anxiolytic clonazepam showed the best results considering the best effect estimate achieving the MID and the moderate certainty. Therefore, this discussion will center on the best results observed from the NMA, the use of clonazepam.

Clonazepam is a gamma-aminobutyric acid agonist designed as an antiepileptic drug. The gamma-aminobutyric acid is the main inhibitory neurotransmitter in development. Its primary role is to reduce neuronal excitability throughout the nervous system and regulate muscle tone (Grushka et al. 1998). The biological plausibility of the positive effect of clonazepam may be linked to the fact that, in patients with BMS, an abnormal blood circulation of the oral mucosa is observed after stimulation with dry ice. This reaction has been interpreted as an abnormal neuromicrovascular regulation, indicating neuropathological involvement at the level of cranial nerves (Heckmann et al. 2001; Heckmann et al. 2012; Tan et al. 2022).

The network included five studies, and two for the comparison against placebo. The first one tested oral clonazepam (Heckmann et al., 2012) and the latter tested its topical application (Gremeau-Richard et al. 2004).

One study did not include a placebo group. Instead, three groups of 30 patients each were treated with: oral clonazepam (2 mg/day), pregabalin (150 mg/day), and ALA (600 mg/day). Oral pain was measured before and after four months of treatment using the visual analogic scale (VAS). Significant improvement was observed only in the clonazepam and pregabalin groups. The authors concluded that systemic clonazepam and pregabalin are viable options for the treatment of BMS (Çınar et al. 2018). The second study with oral clonazepam compared to placebo showed pain relief in patients with BMS. Moreover, clonazepam did not show major side effects that would severely restrict its application (Heckmann et al. 2012). Meanwhile, Gremeau-Richard et al. (2004) conducted a study to assess the effectiveness of topical use of clonazepam. Forty-one patients were instructed to suck a 1 mg tablet of clonazepam or placebo and keep saliva close to the sites of pain in the mouth without swallowing for 3 minutes and then spitting it out. This protocol was repeated three times a day for 14 days. Two weeks after starting treatment, the significant decrease in pain scores was 2.4+/-0.6 and 0.6+/-0.4 in the clonazepam and placebo groups, respectively. It is assumed that clonazepam can act locally to reduce pain in individuals with BMS.

Different treatment routes or dosages for clonazepam (and the other treatments) could render different results. We tried to decrease the intransitivity by separating treatments into four main groups (PBMT, phytotherapics, ALA, anxiolytics/antidepressants). However, some different treatment routes remained, such as for clonazepam (oral and topical). Also there are different dosages as well. To avoid increasing imprecision, we kept together the same treatments independent of the route or dosage. Even though trying to control these problems, imprecision (75%) and intransitivity (78.6%) were the main problems responsible for rating down the certainty of the evidence. The certainty of the evidence was rated down due to risk of bias (30%), inconsistency (10%), and indirectness (55%) (the calculation considered the comparisons with placebo). Few trials were at low risk of bias, and the majority had some

concerns. However, we rated down the certainty of the evidence when one or two trials were at high risk of bias. There was no reason to rate down the certainty of the evidence due to publication bias as no trial was industry-sponsored, and due to incoherence.

Quality of life was measured using the OHIP-14 and OHIP-49. No treatment achieved the MID for quality of life improvement with moderate or high certainty to be considered effective. The evidence is uncertain that clonazepam may improve the quality of life.

The lack of impact on quality of life may be explained by side effects reported by trials. However, there were few side effects. The most frequently reported side effects of the anxiolytics were: dizziness, fever, headache, lack of appetite sleepiness, in accordance with the side effects reported by another study (Arduino et al. 2016). It seems that clonazepam is most effective in low doses in younger individuals and for patients who have had fewer years of symptoms of BMS (Heckmann et al. 2012). When higher doses are required to reduce burning sensation, they appear to be associated with problematic side effects, leading to discontinuation of medication usage (Grushka et al. 1998). In contrast, higher doses of up to 4 mg have also been used with a positive treatment outcome (Heckmann et al. 2012; Huang et al. 1996). However, the included studies did not follow up the patients for long periods to have a more reasonable outcome regarding side effects or quality of life. The longest trial followed up the patients taking clonazepam for 120 days (Çinar et al., 2018), and the shortest one had 14 days of follow-up (Gremeau-Richard et al. 2004). Therefore, our results do not justify the prolonged use of benzodiazepines to treat BMS. In fact, little is known if there was any long-term benefit for these patients (Tan et al. 2022). In addition, the long-term use of benzodiazepines can be especially problematic in older populations (Çınar et al. 2018; Tan et al. 2022).

Strengths and limitations

This is the first NMA in the literature that brings all treatments to treat patients with BMS. Moreover, this review is the most complete so far, as it reports side effects and other primary outcomes.

A limitation is the inclusion of different dosages and treatments vias or the use of other therapies in the same network. The limited sample sizes in each geometry did not fit the optimal information size. Also, the limits of the MID were responsible for rating down the certainty of the evidence due to imprecision in 75% of the cases (Guyatt et al. 2011). Thus, the main limitation of treatments for BMS is the lack of similar treatments with sufficient sample size to create a more precise network. There was also a lack of statistical power due to differences in sample size and number of trials in each comparison (Thorlund and Mills 2012). Furthermore, studies had different follow-up times, and we chose the last time point to calculate the effect estimates. The results could be different if studies were comparable regarding the follow-up time.

On the other side, our review has a robust methodology and uses the minimally and partially contextualized framework to make interpretations of the results. The magnitude of the effect, the certainty of the evidence, and the decision thresholds are conservative and avoid misleading conclusions (Brignardello-Petersen et al. 2018b). This is the first review that brought the MID to interpret results in BMS. The MID is the decision threshold in which treatments should be considered optimal to be chosen by the clinician, considering the acceptability, costs and potential harm to the patient. In this way, the MID is more precise for the decision-making, instead of only considering 95%CI not crossing the null effect line (Carrasco-Labra et al. 2021). From the clinical point of view, this approach considered effective if the treatment could provide minimal effect for the patients (MID) with moderate and high evidence.

Conclusion and implications for research

So far, the best treatment for BMS is the anxiolytic clonazepam. However, the applicability of effectiveness, side effects and quality of life is limited to 120 days (Çınar et al. 2018). Some treatments achieved the MID in reducing pain (PBMT, tongue protector + phytotherapic, pregabalin, phytotherapic). However, the certainty was low and very low, preventing us from endorsing these treatments as we are uncertain if they can deliver minimal effect to the patient. The low and very low certainty in effect estimates indicates that future research is very likely to have an impact on the effect estimates and is likely to change the current evidence (Guyatt et al. 2008).

That being said, and due to the lack of best options to treat BMS, we suggest that future RTCs should investigate different therapeutic techniques compared to placebo. Specifically, the treatments that achieved the MID with low to very low certainty are worth investing in the future. Future trials should also collect data on side effects. Further studies addressing new avenues of research should also be encouraged in the future. Targets specific for calcium channel receptors, G-protein coupled receptors, and regulators of cytokines or immune factors associated with the symptoms of BMS are just some examples of targets unaddressed by current treatments.

Conclusion

The anxiolytic (clonazepam) probably reduces the burning sensation of the BMS. No treatment was able to improve the quality of life of patients. Few studies reported side effects. Moreover, it seems that the side effects did not affect the course of the treatments.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Figure and Tables Legends

Figure 1. PRISMA flowchart of studies screening selection.

Figure 2. Network geometries. Primary outcome – pain (A, B, C, D, E), and secondary outcome – quality of life (F). A. Photobiomodulation therapy (PBMT) network for pain. B. Phytotherapics network for pain. C. Alpha-lipoic acid (ALA) network for pain – continuous outcome. D. Alpha-lipoic acid (ALA) network for pain – binary outcome. E. Anxiolytic and antidepressive network for pain. F. Network for quality of life.

Table 1. Summary of studies characteristics

Table 2. Minimally contextualized framework for the classification of interventions compared to placebo for treatment of burning mouth syndrome (BMS) (primary outcome: pain). Data are presented per network meta-analysis.

Table 3. Partially contextualized framework for the classification of interventions compared to placebo for assessment of quality of life in patients with burning mouth syndrome (BMS) (secondary outcome).

Table 4. Side effects reported by patients.

Table 1. Summary of studies characteristics

Characteristic	**Number or RCTs** 44 (100%)
Continents (authors from)	
Europe[a]	31 (70.45)
South America[b]	5 (11.36)
Asia[c]	4 (9.09)
Middle East[d]	3 (6.81)
North America[e]	1 (2.27)
Language	
English	44 (100)
Year of publication	
1989-1999	3 (6.82)
2000-2009	10 (22.73)
2010-2019	26 (59.09)
2020-2021	5 (11.36)
Funding	
Government/University funding	9 (20.45)
Industry	0 (0)
No funding	6 (13.64)
Not reported	29 (65.91)
Conflict of interest	
yes, the authors report conflict	0 (0)
the authors report no conflict of interests	21 (47.73)
conflict of interest not stated by authors	33 (52.27)
Setting	
Dental school/ hospital	39 (88.64)
Private practice	1 (2.27)
Not reported	4 (9.09)
Number of randomized patients	
Mean (SD)	55.25 (41.56)
Minimum	10
Maximum	200
Total	2,431
Final Sample	
Mean (SD)	51.88 (41.29)
Minimum	10
Maximum	200
Total	2,283
Drop outs	
0 drop outs	25 (56.82)
1 to 10 drop outs	15 (34.09)
>10 drop outs	4 (9.09)
Minimum (n)	0

Maximum (n)	21
Mean Age	
Mean (DP)	64.89 (3.03)
<40 years n (%)	0 (0)
≥40 years n (%)	21 (47.73)
Not reported	23 (52.27)
Minimum	57.5
Maximum	72.65
% of Women	
up to 50% of women in the whole	0 (0)
sample51% to 80% of women in whole sample	18 (40.91)
over 81% of women in whole sample	26 (59.09)
Intervention arms	
2	34 (77.27)
3	5 (11.36)
4	4 (9.09)
5	1 (2.27)
Comparison used in the trial	
Placebo	33 (76.09)
Another treatment	7 (15.22)
The drug test with different doses	2 (4.35)
Control with no intervention/ treatment	2 (4.35)
Treatment duration (Days)	
up to 30 days	20 (45.5)
between 31 and 60 days	13 (29.5)
between 61 and 90 days	7 (15.91)
> 91 days	2 (4.55)
Others[f]	2 (4.55)
Pain scales[g]	
Visual analogue scale 0-10 (VAS)	32 (72.72)
Doesn't mention the name of the scale	6 (13.63)
Numeric rating scale 0-10 (NRS)	4 (9.09)
McGill Pain Questionnaire	2 (4.54)
Others [g,]	6 (13.63)

[a]Italy, Spain, Croatia, France, Germany, Denmark, Serbia, Sweden; [b]Brazil, Argentina; [c] Japan, South Korea, Turkey; [d] Iran, Israel; [e]USA. [f] 84-105 days; 28-70 days. [g]Some studies used more than one scale. The preference for the network meta-analysis was for VAS scale. [h]Total Pain Rating Index (T-PRI): short form of the McGill pain questionnaire; present pain intensity (PPI); visual analogue type scale (VATS); numerical scale especially created for the work; visual numeric scale (VNS); face scale (FS).

Table 2. Minimally contextualized framework for the classification of interventions compared to placebo for treatment of burning mouth syndrome (BMS) (primary outcome: pain). Data are presented per network meta-analysis.

Network meta-analysis for PBMT (7 trials)

P-patients with PBMT

I- PBMT or other treatments

C-placebo

O-pain relief

Beneficial or harmful effect compared to placebo according to MID	Intervention	Intervention versus placebo MD (95% CI)	Ranking	Certainty
Beneficial effect compared to placebo achieving the MID	PBMT	-1.90 (-3.58; -0.21)	0.7441	low
	anxiolytic	-1.89 (-6.72; 2.95)	0.6381	very low

Network meta-analysis for phytotherapics (6 trials)

P-patients with BMS

I- phytoterapics or other treatments

C-placebo

O-pain relief

Beneficial or harmful effect compared to placebo according to MID	Intervention	Intervention versus placebo MD (95% CI)	Ranking	Certainty
Beneficial effect compared to placebo achieving the MID	tongue protector + phytotherapic	-1.37 (-4.29; 1.55)	0.6626	very low
Beneficial effect compared to placebo without achieving the MID	lubricant	-0.95 (-3.72; 1.81)	0.5612	low
	ALA	-0.85 (-3.64; 1.94)	0.5344	very low
	phytotherapic	-0.82 (-2.24; 0.60)	0.5500	very low
	antidepressants	-0.72 (-3.77; 2.34)	0.4995	very low
	tongue protector	-0.50 (-3.36; 2.36)	0.4389	low

Network meta-analysis for ALA (5 trials)

P-patients with BMS

I- ALA or other treatments

C-placebo

O-pain relief

Beneficial or harmful effect compared to placebo according to MID	Intervention	Intervention versus placebo MD (95%CI)	Ranking	Certainty
Beneficial effect compared to placebo achieving the MID	pregabalin	-3.19 (-5.38; -1.00)	0.8947	very low
	anxiolytic	-2.67 (-4.86; -0.47)	0.7742	very low
	phytotherapic	-1.74 (-4.02; 0.55)	0.5954	very low
	lubricant	-1.04 (-3.26; 1.19)	0.4185	low
Beneficial effect compared to placebo without achieving the MID	ALA	-0.19 (-1.42; 1.05)	0.1888	low

Network meta-analysis for ALA (binary outcome, 5 trials)

P-patients with BMS

I- ALA or other treatments

C-placebo

O-pain relief

Beneficial or harmful effect compared to placebo according to MID	Intervention	Intervention versus placebo RR (95%CI)	Ranking	Certainty
Harmful effect compared to placebo achieving the MID	ALA + GABA	4.46 (2.15; 9.27)	0.8174	low
	cognitive therapy + ALA	4.19 (2.14; 8.18)	0.7793	low
	ALA	3.41 (2.26; 5.14)	0.6007	low
	GABA	3.19 (1.43; 7.12)	0.5551	very low
	cognitive therapy	1.85 (0.87; 3.91)	0.2362	very low

Network meta-analysis for anxiolitic and antidepressive (5 trials)

P-patients with BMS

I- anxiolitic and antidepressive or other treatments

C-placebo

O-pain relief

Beneficial or harmful effect compared to placebo according to MID	**Intervention**	**Intervention versus placebo MD (95% CI)**	**Ranking**	**Certainty**
Beneficial effect compared to placebo achieving the MID	pregabalin	- 2.40 (-3.49; -1.32)	0.9074	very low
	PBMT	-1.89 (-4.50; 0.71)	0.7181	very low
	anxiolytic †	-1.88 (-2.61; -1.16)	0.7155	**moderate**
Beneficial effect compared to placebo without achieving the MID	antidepressant	-0.40 (-1.65; 0.85)	0.3600	very low
Harmful effect compared to placebo without achieving the MID	ALA	0.60 (-0.52; 1.71)	0.0600	very low

Random effect model used. MD (mean difference): negative values indicate that the intervention has a beneficial effect when compared to placebo; positive values mean that the intervention has a harmful effect when compared to placebo. MID: minimal important difference; RR (risk ratio): values < 1 indicate that the intervention has a beneficial effect when compared to placebo; values >1 indicate that the intervention has a harmful effect compared to placebo. ALA: alpha lipoic acid. GABA: gabapentin. †Clonazepan.

Table 3. Partially contextualized framework for the classification of interventions compared to placebo for assessment of quality of life in patients with burning mouth syndrome (BMS) (secondary outcome).

Network meta-analysis for treatments for BMS (7 trials)

P-patients with BMS

I- PBMT, anxiolytic, tongue protector, protector + phytotherapic

C-placebo

O-quality of life

Beneficial or harmful effect compared to placebo according to MID	**Intervention**	**Intervention versus placebo SMD (95%CI)**	**Ranking**	**Certainty**
Large beneficial effect compared to placebo	tongue protector and phytotherapic	-0.91 (-1.65; -0.17)	0.9551	low
Small beneficial effect compared to placebo	PBMT	-0.36 (-0.78; 0.05)	0.6851	**moderate**
Trivial or no effect compared to placebo	tongue protector	-0.10 (-0.81; 0.61)	0.4050	low
Trivial or no effect compared to placebo	phytoterapic	-0.03 (-0.70; 0.63)	0.3592	low
Trivial or no harmful effect compared to placebo	anxiolytic	0.05 (-0.86; 0.96)	0.3062	very low

Random effect model used. PBMT: photobiomodulation therapy. SMD (standardized mean difference): negative values indicate that the intervention has a beneficial effect when compared to placebo; positive values mean that the intervention has a harmful effect when compared to placebo. For minimal important difference (MID), the Cohen's classification was used: between -0.2 to 0.2 (trivial or no effect); -0.5 to -0.2 or 0.2 to 0.5 (small effect); -0.8 to -0.5 or 0.5 to 0.8 (moderate effect); <-0.8 or >0.8 (large effect) (Schünemann et al., 2021)

Table 4. Adverse effects reported by patients.

Intervention and dose (sample per intervention)	Side effects (number of patients per intervention)	Study
PBMT 980nm wavelength (18)	0*	Arduino et al. 2016
PBMT 810nm wavelength (10) †	0*	de Pedro et al. 2020
PBMT 685nm wavelength (12)	0*	Skrinjar et al. 2020
PBMT 815nm wavelength (32)	0*	Valenzuela and Lopez-Jornet 2017
ALA 600 mg/day (17)	increase in vitality and wellness (5), improvement in dysgeusia (1), improvement in dry sensation (2), drowsiness (1), gastric complaints (6), headache (4), increase in blood pressure (1), hungriness (1), skin erythema (0)	Cavalcanti and da Silveira 2009
ALA 600 mg/day (21)	0*	Femiano et al. 2000
ALA 600 mg/day (30)	0*	Femiano et al. 2002
ALA 600 mg/day (25)	nausea (2), myalgia (1)	Çınar et al. 2018
ALA 800mg/day (23)	gastrointestinal upset (1)	López-Jornet et al. 2009
ALA 400 mg (14)	0*	Marino et al. 2010
Phytoterapuic Sai-boku-to 7.5g/day (100)	loss of appetite (3), diarrhea (1)	Bessho et al. 1998
Phytoterapic hypericum perforatum 900mg/day (19)	severe headache (1), somnolence (1), weight gain (1), insomnia (1)	Sardella et al. 2008
Capsaicin 0,025% three times daily (22)	strong burning and unpleasant taste after gel application that disappeared after 5 to 30 min after the application (18); nausea, itching, unpleasant consistency of the gel (3)†; soreness of the throat (1) †.	Jørgensen et al. 2016
Aloe vera (24)	0*	López-Jornet et al. 2013
Capsaicin 3.54 μg⁄ml, three times daily (14)	0*	Marino et al. 2010
Crocin (26)	0*	Pakfetrat et al. 2019
Capsaicin 0.02%, 3times /day (12)	0*	Silvestre et al. 2012
Chamomile 2%, twice a day	0*	Valenzuela et al. 2016
Catuama (30)	Somnolence and weight gain (1), insomnia (1), exacerbation of the symptoms (2)	Spanemberg et al. 2012b
Um-PEA 600 mg/twice daily (13)	0*	Ottaviani et al. 2019
Anxiolytic topical clonazepam 3mg/day (15)	dizziness, fever, headache, lack of appetite (5)	Arduino et al. 2016
Anxiolytic oral diazepam 6mg/day (100)	sleepiness (33)	Bessho et al. 1998
Anxiolytic oral clonazepam 2mg/day (25)	dizziness (4), diarrhea (2), myalgia (2)	Çınar et al. 2018

Anxiolytic topical clonazepam 3mg/day (22)	drowsiness (4), burning increase (2), dry mouth (1), spasmophilia (1), euphoric behavior (1)	Gremeau-Richard et al. 2004
Anxiolytic oral clonazepam 0,5mg/day (22)	drowsiness, dizziness, nausea (5)	Jurisic et al. 2015
Antidepressant vortioxetine15mg/day (29)	nausea (3)	Adamo et al. 2020
Antidepressant paroxetine 20 mg/day (25)	weight gain (7), sexual dysfunction (3)	Adamo et al. 2020
Antidepressant sertraline 50mg/day (28)	abdominal pain (2), dizziness (1), weight gain (2), appetite stimulation (1), sexual disfuction (1)	Adamo et al. 2020
Antidepressant escitalopram 10mg/day (26)	nausea (1), abdominal pain (5), QTc prolongation (4), somnolence (2), sexual disfuction (2)	Adamo et al. 2020
Antidepressant duloxetine 60mg/day (26)	dry mouth (1), dizziness (3), elevated serum prolactin (1), somnolence (2), weight gain (2), appetite stimulation (1), sexual dysfunction (1), vivid dreams (1)	Adamo et al. 2020
Antidepressant fluoxetine 20mg/day (50)	Transitory nausea, sporadic headache and dizziness (10)	Zoric et al. 2018
Pregabalin 150mg/day (25)	increased appetite (3), transient vertigo (1), mild nausea (1), diarrhea (1)	Çınar et al. 2018
Topical lubricant with oral rinse 5 times/day (14)	0*	Marino et al., 2010
Acupuncture 3 times/week (20)	0*	Jurisic et al. 2015
Benzydamine 15ml - 0.15%, 3 times/day (10)	0*	Sardella et al. 1999
Electromagnetic stimulus 1 session/day (12)	headache (7)	Umezaki et al. 2016
Melatonine 12mg/day (6)	sleep disturbances (5), headache (1), dizziness (1), impaired concentration (1), appetite alteration (1)	Varoni et al. 2018
Lafutidine 20mg/day (34)	náusea (1), mild abdominal distension (1)	Toida et al. 2009

PBMT: photobiomodulation therapy; ALA: alpha-lipoic acid; GABA: gabapentin. QTc prolongation (measurement of delayed ventricular repolarization).*0: no patients complained of side effects. †Patients dropped the treatment.

Figure 1 - PRISMA flowchart of studies screening selection.

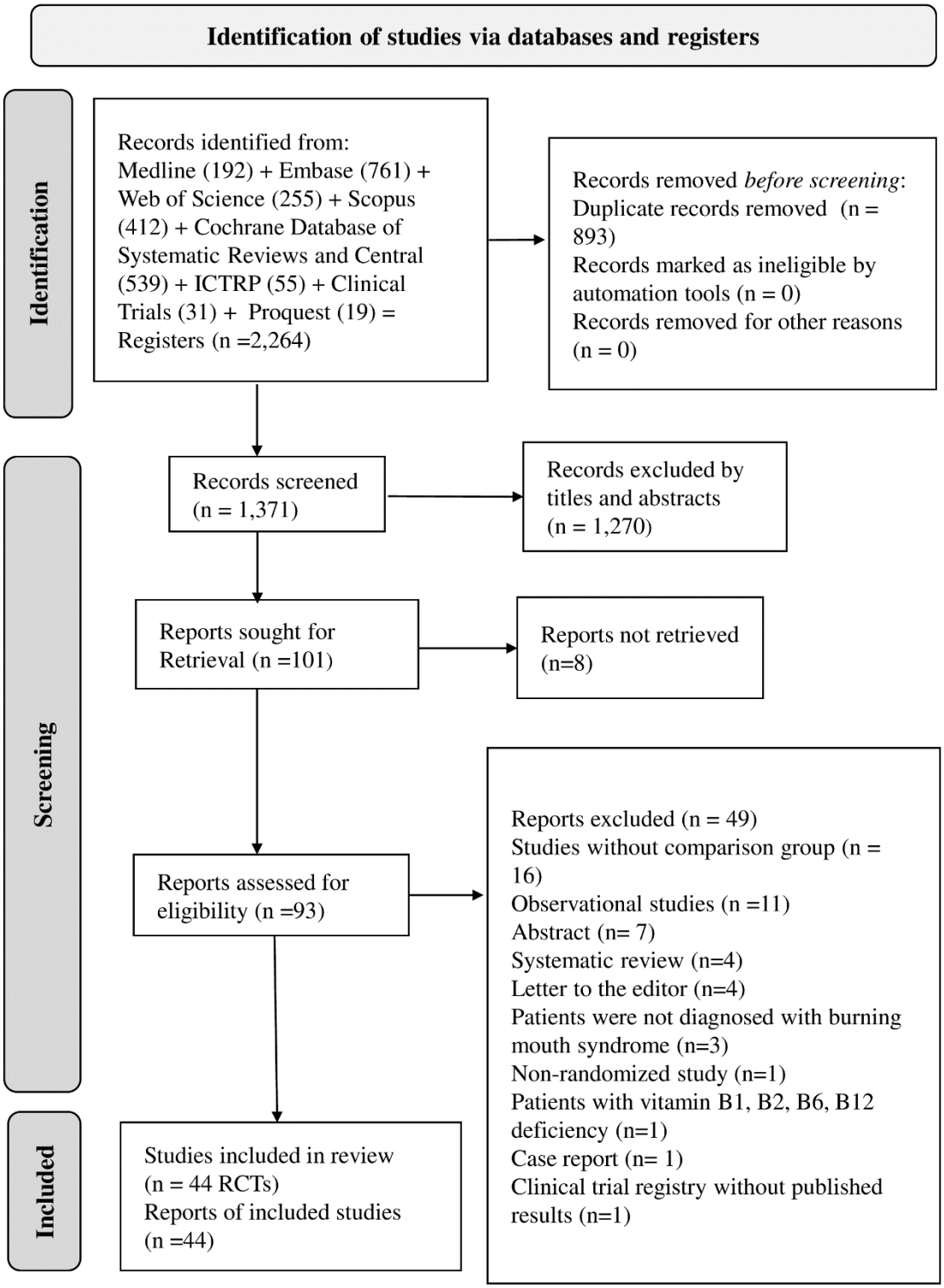
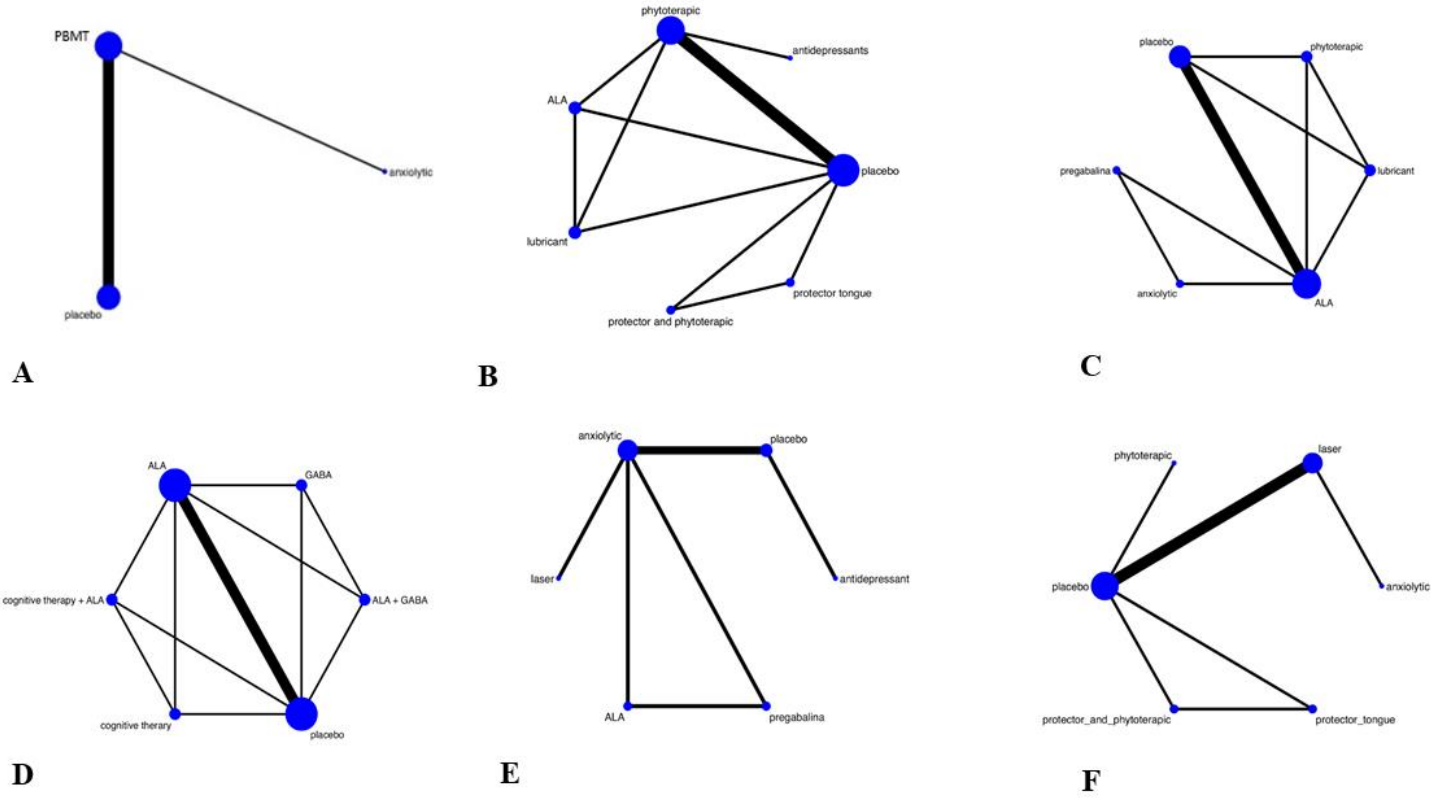


Figure 2 - Network geometries. Primary outcome – pain (A, B, C, D, E), and secondary outcome – quality of life (F). A. Photobiomodulation therapy (PBMT) network for pain. B. Phytotherapics network for pain. C. Alpha-lipoic acid (ALA) network for pain – continuous outcome. D. Alpha-lipoic acid (ALA) network for pain – binary outcome. E. Anxiolytic and antidepressive network for pain. F. Network for quality of life.



Appendix Table 1. Search strategies used according to electronic databases (date: from interception to February 2021, updated in December 2021).

MedLine through Ovid

1. burning mouth syndrome.mp. or exp Burning Mouth Syndrome/
2. burning mouth.mp.
3. treatment*.mp.
4. therap*.mp.
5. capsaicin.mp. or Capsaicin/
6. melatonin.mp. or Melatonin/
7. exp Hyperalgesia/ or exp Ethanolamines/ or exp Analgesics/ or ultramicronized palmitoylethanolamide.mp. or exp Anti-Inflammatory Agents, Non-Steroidal/
8. palmitoylethanolamide.mp.
9. Plant Extracts/ or hypericum perforatum extract.mp.
10. hypericum perforatum.mp.
11. exp Plants, Medicinal/ or exp Phytotherapy/ or exp Drugs, Chinese Herbal/ or exp Plant Extracts/ or herbal compound*.mp.
12. catuama.mp.
13. Matricaria/ or chamomile.mp. or Chamomile/
14. matricaria chamomilla.mp. or Matricaria/
15. matricaria recutita.mp.
16. exp Aloe/ or aloe vera barbadensis.mp.
17. aloe vera.mp. or Aloe/
18. alpha lipoic acid.mp.
19. low-level laser therapy.mp. or exp Low-Level Light Therapy/
20. exp Laser Therapy/ or laser therap*.mp.
21. low-level laser.mp.
22. photobiomodulation therapy.mp.
23. photobiomodulation.mp. or exp Phototherapy/
24. exp Acupuncture, Ear/ or auriculotherapy.mp. or exp Auriculotherapy/ or exp Acupuncture Therapy/
25. acupuncture.mp.
26. anxiolytic.mp. or exp Anti-Anxiety Agents/
27. anti-anxiety agent*.mp.

28. fluoxetine.mp. or exp Fluoxetine/
29. clonazepam.mp. or exp Clonazepam/
30. Benzodiazepines/ or benzodiazepine*.mp.
31. serotonin uptake inhibitors.mp. or Serotonin/ or Serotonin Uptake Inhibitors/
32. paroxetine.mp. or Paroxetine/
33. sertraline.mp. or Sertraline/
34. milnacipran.mp. or Milnacipran/
35. gabapentin.mp. or Gabapentin/
36. exp Antidepressive Agents/ or antidepress*.mp.
37. drug therapy.mp. or exp Drug Therapy/
38. herbal medicine.mp. or exp Herbal Medicine/ or exp Medicine, Chinese Traditional
39. homeopathy.mp. or exp Homeopathy/
40. trazodone.mp.
41. bupivacaine.mp. or exp Bupivacaine/
42. extra virgin olive oil.mp.
43. olive oil.mp. or exp Olive Oil/
44. lycopene.mp. or exp Lycopene/
45. exp Urea/ or urea.mp.
46. benzydamine hydrochloride.mp. or exp Benzydamine/
47. randomized controlled.mp.
48. randomized controlled trial.mp. or exp Randomized Controlled Trial/
49. randomized controlled trial*.mp.
50. controlled clinical trial.mp. or exp Controlled Clinical Trial/
51. exp Random Allocation/ or random*.mp.
52. randomized.mp.
53. placebo.mp.
54. randomly.mp.
55. groups.mp.
56. exp Clinical Trial/ or trial.mp.
57. meta-analysis.mp. or exp Meta-Analysis/
58. systematic review*.mp.
59. randomization.mp.
60. 1 or 2

61. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
62. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
63. 60 and 61 and 62

Embase through Ovid

#1. ('burning'/exp OR burning) AND ('mouth'/exp OR mouth) AND ('syndrome'/exp OR syndrome)
#2. burning AND mouth
#3. 'drug therapy'
#4. capsaicin*
#5. melatonin*
#6. ultramicronized AND palmitoylethanolamide
#7. palmitoylethanolamide
#8. hypericum AND perforatum AND extract
#9. hypericum AND perforatum
#10. herbal AND compound
#11. catuama
#12. chamomile
#13. matricaria AND chamomilla
#14. 'matricaria chamomilla extract'
#15. matricaria AND recutita
#16. aloe AND vera AND barbadensis
#17. aloe AND vera
#18. 'aloe vera extract'
#19. alpha AND lipoic AND acid
#20. 'low level' AND laser AND therapy
#21. laser AND therapy
#22. 'low level' AND laser
#23. photobiomodulation AND therapy
#24. photobiomodulation
#25. auriculotherapy

#26. 'auricular acupuncture'
#27. acupuncture
#28. 'acupuncture analgesia'
#29. anxiolytic
#30. 'anti anxiety' AND agent*
#31. 'fluoxetine'
#32. 'clonazepam'
#33. benzodiazepines
#34. serotonin AND uptake AND inhibitor*
#35. 'paroxetine'
#36. 'sertraline'
#37. 'milnacipran'
#38. gabapentin
#39. 'antidepress* agent*'
#40. antidepress*
#41. drug AND therap*
#42. herbal AND medicine
#43. homeopath*
#44. trazodone
#45. 'bupivacaine'
#46. bupivacaine AND lozenge
#47. olive AND oil
#48. 'extra virgin olive oil'
#49. 'lycopene'
#50. 'urea'
#51. benzydamine AND hydrochloride AND oral AND rinses
#52. 'benzydamine'
#53. benzydamine AND hydrochloride
#54. 'treatment'
#55. 'therapy'
#56. 'randomized controlled trial'
#57. randomized AND controlled
#58. random AND allocation

#59. 'controlled clinical trial'

#60. trial*

#61. 'clinical trial'

#62. random*

#63. 'randomization'

#64. randomized

#65. randomly

#66. 'placebo'

#67. 'meta analysis'

#68. systematic AND review*

#69. #1 OR #2

#70. #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55

#71. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68

#72. #69 AND #70 AND #71

Cochrane Database of Systematic Reviews and CENTRAL

#1	burning mouth syndrome
#2	burning mouth
#3	#1 OR #2
#4	treatment*
#5	therap*
#6	'drug therapy'
#7	capsaicin*
#8	melatonin*
#9	ultramicronized AND palmitoylethanolamide
#10	palmitoylethanolamide
#11	hypericum AND perforatum
#12	MeSH descriptor: [Hypericum] explode all trees

#13	herbal AND compound
#14	catuama
#15	chamomile
#16	matricaria AND chamomilla
#17	'matricaria chamomilla extract'
#18	matricaria AND recutita
#19	aloe AND vera AND barbadensis
#20	aloe AND vera
#21	'aloe vera extract'
#22	alpha AND lipoic AND acid
#23	'low level' AND laser AND therapy
#24	MeSH descriptor: [Low-Level Light Therapy] explode all trees
#25	laser AND therapy
#26	MeSH descriptor: [Laser Therapy] explode all trees
#27	'low level' AND laser
#28	photobiomodulation AND therapy
#29	photobiomodulation
#30	'auricular acupuncture'
#31	MeSH descriptor: [Auriculotherapy] explode all trees
#32	acupuncture
#33	'acupuncture analgesia'
#34	anxiolytic
#35	'anti anxiety' AND agent*
#36	'fluoxetine'
#37	'clonazepam'
#38	benzodiazepines
#39	MeSH descriptor: [Benzodiazepines] explode all trees
#40	serotonin AND uptake AND inhibitor*
#41	MeSH descriptor: [Serotonin] explode all trees
#42	'paroxetine'
#43	'sertraline'
#44	'milnacipran'
#45	MeSH descriptor: [Milnacipran] explode all trees

#46	gabapentin
#47	antidepress*
#48	'antidepress* agent*'
#49	MeSH descriptor: [Antidepressive Agents] explode all trees
#50	drug AND therap*
#51	MeSH descriptor: [Drug Therapy] explode all trees
#52	herbal AND medicine
#53	homeopath*
#54	Trazodone
#55	Bupivacaine lozenge
#56	Bupivacaine
#57	MeSH descriptor: [Bupivacaine] explode all trees
#58	Olive oil
#59	Extra virgin olive oil
#60	lycopene
#61	Urea
#62	MeSH descriptor: [Urea] explode all trees
#63	Benzydamine hydrochloride oral rinses
#64	Benzydamine hydrochloride
#65	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64
#66	randomized AND controlled
#67	randomized AND controlled AND trial*
#68	MeSH descriptor: [Random Allocation] explode all trees
#69	controlled AND clinical AND trial
#70	trial*
#71	clinical AND trial
#72	random*
#73	randomized

#74 randomly

#75 randomization

#76 placebo

#77 MeSH descriptor: [Placebos] explode all trees

#78 'meta analysis'

#79 systematic AND review*

#80 #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79

#81 #3 AND #65 AND #80

Web of Science

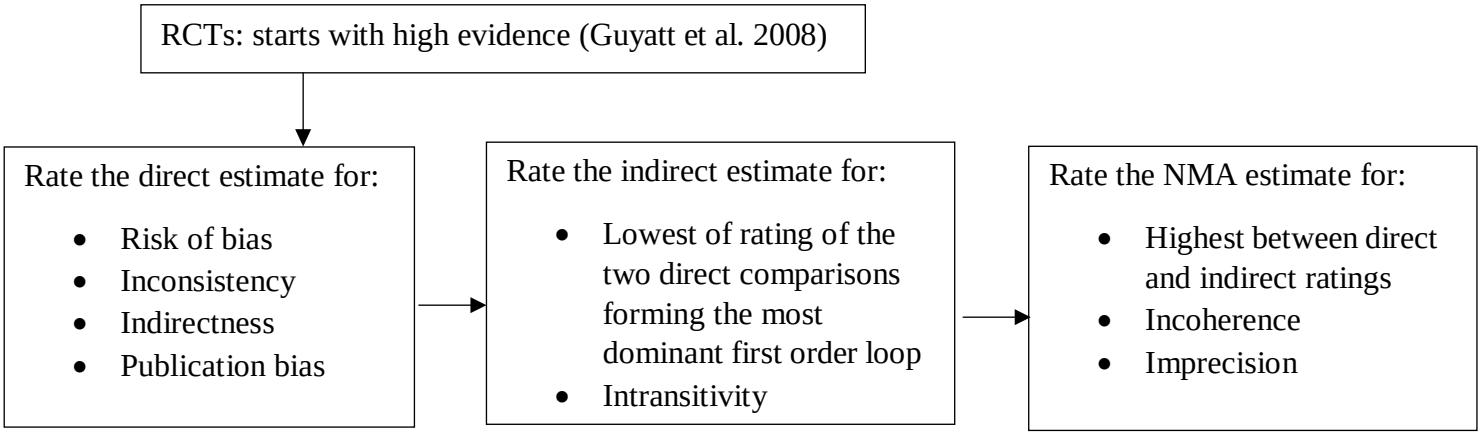
TS=(("burning mouth syndrome" OR "burning mouth") AND (treatment* OR therap* OR "drug therap*" OR capsaicin* OR melatonin* OR "ultramicronized palmitoylethanolamide" OR palmitoylethanolamide OR "hypericum perforatum extract" OR "hypericum perforatum" OR "herbal compound" OR catuama OR chamomile OR "matricaria chamomilla" OR "matricaria chamomilla extract" OR "matricaria recutita" OR "aloe vera barbadensis" OR "aloe vera" OR "aloe vera extract" OR "alpha lipoic acid" OR "low level laser therap*" OR "laser therap*" OR "low level laser" OR "photobiomodulation therap*" OR photobiomodulation OR "auriculotherap*" OR "auricular acupuncture" OR acupuncture OR "acupuncture analgesia" OR anxiolytic OR "anti anxiety agent*" OR fluoxetine OR clonazepam OR benzodiazepines OR "serotonin uptake inhibitor*" OR paroxetine OR sertraline OR milnacipran OR gabapentin OR "antidepress* agent*" OR antidepress* OR "herbal medicine" OR homeopath* OR trazodone OR 'bupivacaine' OR "bupivacaine lozenge" OR "olive oil" OR "extra virgin olive oil" OR lycopene OR urea OR "benzydamine hydrochloride oral rinses" OR benzydamine OR "benzydamine hydrochloride") AND ("randomized controlled" OR randomization OR "randomized controlled trial*" OR "controlled clinical trial" OR trial* OR "clinical trial*" OR random* OR randomized OR randomly OR placebo OR groups OR "meta analysis" OR "systematic review*"))

Scopus

TITLE-ABS-KEY ("burning mouth syndrome" OR "burning mouth") AND TITLE-ABS-KEY (treatment* OR therap* OR "drug therap*" OR capsaicin* OR melatonin* OR "ultramicronized palmitoylethanolamide" OR palmitoylethanolamide OR

"hypericum perforatum extract" OR "hypericum perforatum" OR "herbal compound" OR catuama OR chamomile OR "matricaria chamomilla" OR "matricaria chamomilla extract" OR "matricaria recutita" OR "aloe vera barbadensis" OR "aloe vera" OR "aloe vera extract" OR "alpha lipoic acid" OR "low level laser therap*" OR "laser therap*" OR "low level laser" OR "photobiomodulation therap*" OR photobiomodulation OR "auriculotherap*" OR "auricular acupuncture" OR acupuncture OR "acupuncture analgesia" OR anxiolytic OR "anti anxiety agent*" OR fluoxetine OR clonazepam OR benzodiazepines OR "serotonin uptake inhibitor*" OR paroxetine OR sertraline OR milnacipran OR gabapentin OR "antidepress* agent*" OR antidepress* OR "herbal medicine" OR homeopath* OR trazodone OR 'bupivacaine' OR "bupivacaine lozenge" OR "olive oil" OR "extra virgin olive oil" OR lycopene OR urea OR "benzydamine hydrochloride oral rinses" OR benzydamine OR "benzydamine hydrochloride") AND TITLE-ABS-KEY ("randomized controlled" OR "randomizedntrolled trial*" OR randomization OR "controlled clinical trial" OR trial* OR "clinical trial*" OR random* OR randomized OR randomly OR placebo OR groups OR "meta analysis" OR "systematic review*")
The WHO International Clinical Trials Registry Plataform (ICTRP) https://www.who.int/ictrp/en/ (burning mouth syndrome)
Clinical Trials https://clinicaltrials.gov/ (burning mouth syndrome)
Dissertation database (ProQuest Dissertation and theses database) (burning mouth syndrome)

Appendix Flowchart 1. Certainty of evidence assessed through GRADE approach for networkmeta-analysis (NMA) (Bonner et al. 2018; Brignardello-Petersen et al. 2018a; Puhan et al. 2014)



Appendix Table 2. Description of criteria used to assess the certainty of evidence.

	Rated down direct estimate if:
Risk of bias	The risk of bias was rated down if one or more studies were at an overall high risk of bias (Bonner et al. 2018).
Inconsistency	If effect estimates varied across studies (Guyatt et al. 2011); Lack of overlap of 95%Crl (Guyatt et al. 2011); I^2 for direct comparisons was either moderate (30-60%), substantial (50-90%) or considerable (75%-100%) (Higgins J. P. T. 2019). When a single study was included in a comparison, the inconsistency was not rated down (Guyatt et al. 2011);.
Indirectness	Indirectness was assessed considering the applicability of intervention according to the clinical question (protocol or dose of the intervention) (Bonner et al. 2018; Brignardello-Petersen et al. 2018a; Puhan et al. 2014). For photobiomodulation therapy (PBMT), the indirectness was rated down due to the lack of applicability of different protocols (e.g., different wavelengths such as 630 nm, 685 nm, 810 nm) For anxiolytics and antidepressants and phytoterapics, the indirectness was rated down when single drugs formed the evidence. E.g. when clonazepam was the only antidepressant for the comparison, with limited applicability for all antidepressants. For alpha-lipoic acid (ALA) and gabapentin (GABA), we considered indirectness when a single dosage was considered for the evidence, limiting the applicability to other drug dosages. We did not find differences in the protocol for cognitive therapy to rate down the certainty.
Publication bias	Industry funding was considered for publication bias. The decision to rate down due to publication bias is if more than 70% of the weight of the pooled effect estimate comes from studies funded by the industry for which the pooled estimate shows favorable evidence (Bonner et al. 2018). In this NMAs, no study was industry-funded, so the certainty was not rated down due to publication bias.
	Rated down indirect estimate if:

Intransitivity	For intransitivity, we assessed the most dominant first-order loop. We considred the criteria for indirectness described above. We evaluated if the evidence coming from the two direct comparisons of the loop could modify the treatment effect that formed the indirect estimate of the loop (Puhan et al. 2014).
	Rated down NMA estimate if:
Incoherence	Incoherence was assessed by comparing direct estimates, indirect estimates and the network estimate using the back-calculation method (Lu and Ades 2012). Whenever the p-value was >0.05, the incoherence was not serious, and incoherence was not rated down. If the direct and network estimates pointed out in the same direction, the certainty was not rated down even if p<0.05. The certainty of the evidence was rated down if p<0.05, and the direct estimate pointed out in the opposite direction of the indirect estimate and the network estimate (Puhan et al. 2014).
Imprecision	For imprecision, we considered the minimal important difference (MID) necessary to a treatment decision comparing intervention and placebo (comparator) (Brignardello-Petersen et al. 2018b). If the 95%CI crossed the decision threshold of the MID, the certainty of the evidence was rated down in one level; and in two levels if the 95%CI also crossed the line of null effect. If the effect estimate of intervention was higher or lower than the MID, the intervention was considered beneficial or harmful compared to placebo, according to the direction of the effect estimate (Brignardello-Petersen et al. 2018a). For pain (mean difference – MD), the threshold for MID was -1.0 or 1.0 (Dworkin et al. 2009), and 0.32 or 1.68 for risk ratio (RR) (Chen et al. 2010). For MD, negative values indicate that the intervention has a beneficial effect when compared to placebo; positive values mean that the intervention has a detrimental effect when compared to placebo. For RR: values greater than 1 indicate that the intervention has a harmful effect when compared to placebo; values <1 indicate that the intervention has a beneficial effect when compared to placebo. For the secondary outcome "quality of life", the Cohen classification was used for standardized mean difference (SMD): between -0.2 to 0.2 (trivial or no effect); -0.5 to -0.2 or 0.2 to 0.5 (small effect); -0.8 to -0.5 or 0.5 to 0.8 (moderate effect); <-0.8 or >0.8 (large effect) (Schünemann HJ 2021). The large effect was the MID for benefit or harm effect. Negative values indicate that the intervention has a beneficial effect when

	compared to placebo; positive values mean that the intervention has a detrimental effect when compared to placebo.

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Kho HS, Lee JS, Lee EJ, Lee JY. 2010. The effects of parafunctional habit control and topical lubricant on discomforts associated with burning mouth syndrome (bms). Arch Gerontol Geriatr. 51(1):95-99.

López-D'alessandro E, Escovich L. 2011. 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. 16(5):e635-e640.

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

López-Jornet P, Camacho-Alonso F, Molino-Pagan D. 2013. Prospective, randomized, double-blind, clinical evaluation of aloe vera barbadensis, applied in combination with a tongue protector to treat burning mouth syndrome. J Oral Pathol Med. 42(4):295-301.

Marino R, Torretta S, Capaccio P, Pignataro L, Spadari F. 2010. Different therapeutic strategies for burning mouth syndrome: Preliminary data. J Oral Pathol Med. 39(8):611-616.

Ottaviani G, Rupel K, Gobbo M, Poropat A, Zoi V, Faraon M, Di Lenarda R, Biasotto M. 2019. Efficacy of ultramicronized palmitoylethanolamide in burning mouth syndrome-affected patients: A preliminary randomized double-blind controlled trial. Clin Oral Investig. 23(6):2743-2750.

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

Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, Llamas-Martínez S, Esparza-Gómez G. 2015. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. Med Oral Patol Oral Cir Bucal. 20(4):e435-e440.

Pezelj-Ribarić S, Kqiku L, Brumini G, Urek MM, Antonić R, Kuiš D, Glažar I, Städtler P. 2013. Proinflammatory cytokine levels in saliva in patients with burning mouth syndrome before and after treatment with low-level laser therapy. Lasers Med Sci. 28(1):297-301.

Sardella A, Lodi G, Demarosi F, Tarozzi M, Canegallo L, Carrassi A. 2008. Hypericum perforatum extract in burning mouth syndrome: A randomized placebo-controlled study. J Oral Pathol Med. 37(7):395-401.

Sardella A, Uglietti D, Demarosi F, Lodi G, Bez C, Carrassi A. 1999. Benzydamine hydrochloride oral rinses in management of burning mouth syndrome: A clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 88(6):683-686.

Scardina GA, Casella S, Bilello G, Messina P. 2020. Photobiomodulation therapy in the management of burning mouth syndrome: Morphological variations in the capillary bed. Dent J. 8(3):99.

Sikora M, Včev A, Siber S, Boras VV, Rotim Ž, Matijević M. 2018. The efficacy of low-level laser therapy in burning mouth syndrome - a pilot study. Acta Clin Croat. 57(2):312-315.

Silvestre FJ, Silvestre-Rangil J, Tamarit-Santafé C, Bautista D. 2012. Application of a capsaicin rinse in the treatment of burning mouth syndrome. Med Oral Patol Oral Cir Bucal. 17(1):e-e4.

Skrinjar I, Brzak BL, Vidranski V, Boras VV, Andabak Rogulj A, Pavelic B. 2020. Salivary cortisol levels and burning symptoms in patients with burning mouth syndrome before and after low level laser therapy: A double blind controlled randomized clinical trial. Acta Stomatol Croat. 54(1):44-50.

Spanemberg JC, Cherubini K, de Figueiredo MA, Gomes AP, Campos MM, Salum FG. 2012. 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. 113(3):373-377.

Spanemberg JC, López JL, De Figueiredo MAZ, Cherubini K, Salum FG. 2015. Efficacy of low-level laser therapy for the treatment of burning mouth syndrome: A randomized, controlled trial. J Biomed Opt. 20(9):098001.

Spanemberg JC, Segura-Egea JJ, Rodríguez-de Rivera-Campillo E, Jané-Salas E, Salum FG, López-López J. 2019. Low-level laser therapy in patients with burning mouth syndrome: A double-blind, randomized, controlled clinical trial. J Clin Exp Dent. 11(2):e162-e169.

Sugaya NN, da Silva EFP, Kato IT, Prates R, Gallo CD, Pellegrini VD. 2016. Low intensity laser therapy in patients with burning mouth syndrome: A randomized, placebo-controlled study. Braz Oral Res. 30(1):e108.

Toida M, Kato K, Makita H, Long NK, Takeda T, Hatakeyama D, Yamashita T, Shibata T. 2009. Palliative effect of lafutidine on oral burning sensation. J Oral Pathol Med. 38(3):262-268.

Umezaki Y, Badran BW, Devries WH, Moss J, Gonzales T, George MS. 2016. The efficacy of daily prefrontal repetitive transcranial magnetic stimulation (rtms) for burning mouth syndrome (bms): A randomized controlled single-blind study. Brain Stimul. 9(2):234-242.

Valenzuela S, Lopez-Jornet P. 2017. Effects of low-level laser therapy on burning mouth syndrome. J Oral Rehabil. 44(2):125-132.

Valenzuela S, Pons-Fuster A, López-Jornet P. 2016. Effect of a 2% topical chamomile application for treating burning mouth syndrome: A controlled clinical trial. J Oral Pathol Med. 45(7):528-533.

Varoni EM, Faro AFL, Lodi G, Carrassi A, Iriti M, Sardella A. 2018. Melatonin treatment in patients with burning mouth syndrome: A triple-blind, placebo-controlled, crossover randomized clinical trial. J Oral Facial Pain Headache. 32(2):178-188.

Zoric B, Jankovic L, Kuzmanovic PJ, Zidverc-Trajkovic J, Mijajlovic M, Stanimirovic D. 2018. The efficacy of fluoxetine in bms—a cross-over study. Gerodontology. 35(2):123-128.

Appendix Table 3. Studies excluded after full text analysis and reasons for exclusion.

Study	Reason for exclusion
Adamo D, Ruoppo E, Celentano A, Aria M, Leuci S, Mignogna MD. 2016. Antipsychotics in the treatment of burning mouth syndrome. Oral Dis. 22:16.	Abstract.
Alessio G, Evangelos P, Marco C, Adriana C, Roberto B, Giacomo AP. 2019. Usefulness of a cannabis-based medication in patients with burning mouth syndrome: Preliminary results of a prospective pilot study. J Oral Pathol Med. 48:20.	Abstract
Aitken-Saavedra J, Chaves Tarquinio SB, De Oliveira Da Rosa WL, Fernandes Da Silva A, Almeida MacHado BM, Santos Castro I, Oliveira Wennesheimer A, Morales-Bozo I, Uchoa Vasconcelos AC, Neutzling Gomes AP. 2020. Effect of a homemade salivary substitute prepared using chamomile matricaria chamomilla l. Flower and flax linum usitatissimum l. Seed to relieve primary burning mouth syndrome: A preliminary report. J Altern Complement Med. 26(9):799-806.	Study without a comparison group.
Al-Maweri SA, Javed F, Kalakonda B, AlAizari NA, Al-Soneidar W, Al-Akwa A. 2017. Efficacy of low level laser therapy in the treatment of burning mouth syndrome: A systematic review. Photodiagnosis Photodyn Ther. 17:188-193.	A systematic review of the literature.
Antonić R, Brumini M, Vidović I, Urek MM, Glažar I, Pezelj-Ribarić S. 2017. The effects of low level laser therapy on the management of chronic idiopathic orofacial pain: Trigeminal neuralgia, temporomandibular disorders and burning mouth syndrome. Medicina Flum. 53(1):61-67.	Study without a comparison group.
Aravindhan R, Vidyalakshmi S, Kumar M, Satheesh C, Balasubramanium A, Prasad VS. 2014. Burning mouth syndrome: A review on its diagnostic and therapeutic approach. J Pharm Bioallied Sci. 6:S21-S25.	A systematic review of the literature.

Ariyawardana A, Chmieliauskaite M, Farag AM, Albuquerque R, Forssell H, Nasri-Heir C, Klasser GD, Sardella A, Mignogna MD, Ingram M et al. 2019. World workshop on oral medicine vii: Burning mouth syndrome: A systematic review of disease definitions and diagnostic criteria utilized in randomized clinical trials. Oral Dis. 25(S1):141-156.	A systematic review of the literature.
Ayuse T, Okayasu I, Tachi-Yoshida M, Sato J, Saisu H, Shimada M, Yamazaki Y, Imura H, Hosogaya N, Nakashima S. 2020. Examination of pain relief effect of goreisan for glossodynia. Medicine. 99(33):e21536.	Clinical trial registry without published results.
Azzi L, Veronesi G, Tagliabue A, Croveri F, Maurino V, Reguzzoni M, Tettamanti L, Protasoni M, Spadari F. 2019. Is there an association between drugs and burning mouth syndrome? A case–control study. Oral Dis. 25(6):1634-1644.	Observational study.
Baad-Hansen L, Staehelin-Jensen T, Svensson P. 2003. A human model of intraoral pain and heat hyperalgesia. J Orofac Pain. 17(4):333-340.	Patients were not diagnosed with burning mouth syndrome.
Barbosa NG, Gonzaga AKG, de Sena Fernandes LL, da Fonseca AG, Queiroz S, Lemos T, da Silveira É, de Medeiros AMC. 2018. Evaluation of laser therapy and alpha-lipoic acid for the treatment of burning mouth syndrome: A randomized clinical trial. Lasers Med Sci. 33(6):1255-1262.	Patients were not diagnosed with burning mouth syndrome.
Barker KE, Batstone MD, Savage NW. 2009. Comparison of treatment modalities in burning mouth syndrome. Aust Dent J. 54(4):300-305.	Observational study.
Bhoopathi V, Mascarenhas AK. 2011. Zinc-replacement therapy may not reduce oral pain in patients with zinc-deficient burning mouth syndrome (bms). J. Evid. Based Dent. Pract. 11(4):189-190.	A systematic review of the literature.

Bogetto F, Ferro G, Maina G, Gandolfo S. 1997. Amisulpride vs paroxetine in the treatment of burning mouth syndrome (bms). Sixth world congress of biological psychiatry, nice, france June 22-27, 1997.	Abstract.
Boras VV, Canjuga I, Brailo V, Juras DV. 2011. The effect of topical hyaluronic acid in patients with burning mouth syndrome. Acta Stomatol Croat. 45(2):141.	Abstract.
Brailo V, Bosnjak A, Boras VV, Jurisic AK, Pelivan I, Kraljevic-Simunkovic S. 2013. Laser acupuncture in the treatment of burning mouth syndrome: A pilot study. Acupunct Med. 31(4):453-454.	Study without a comparison group.
Cho D, Jee H, Je H. 2012. Treatment of glossodynia (burning mouth syndrome) with quetiapine. Eur Neuropsychopharmacol. 22:S323-S324.	Case report.
Daniela A, Giuseppe P, Giulio F, Elvira R, Roberto C, Michele M. 2019. Vortioxetine in the treatment of mood disorders associated with burning mouth syndrome: Results of an open label, flexible-dose pilot study. J Oral Pathol Med.. 48:21.	Observational study.
de Castro LA, Ribeiro-Rotta RF. 2014. The effect of clonazepam mouthwash on the symptomatology of burning mouth syndrome: An open pilot study. Pain Med. 15(12):2164-2166.	Letter to the editor.
dos Santos Lde F, de Andrade SC, Nogueira GE, Leao JC, de Freitas PM. 2015. Phototherapy on the treatment of burning mouth syndrome: A prospective analysis of 20 cases. Photochem Photobiol. 91(5):1231-1236.	Study without a comparison group.
Femiano F, Scully C, Gombos F. 2002. Idiopathic dysgeusia; an open trial of alpha lipoic acid (ala) therapy. International Journal of Oral and Maxillofacial Surgery. 31(6):625-628.	Patients were not diagnosed with burning mouth syndrome.
Fenelon M, Quinque E, Arrive E, Catros S, Fricain JC. 2017. Pain-relieving effects of clonazepam and amitriptyline in burning mouth syndrome: A retrospective study. J. Oral Maxillofac. Surg. 46(11):1505-1511.	Observational study.

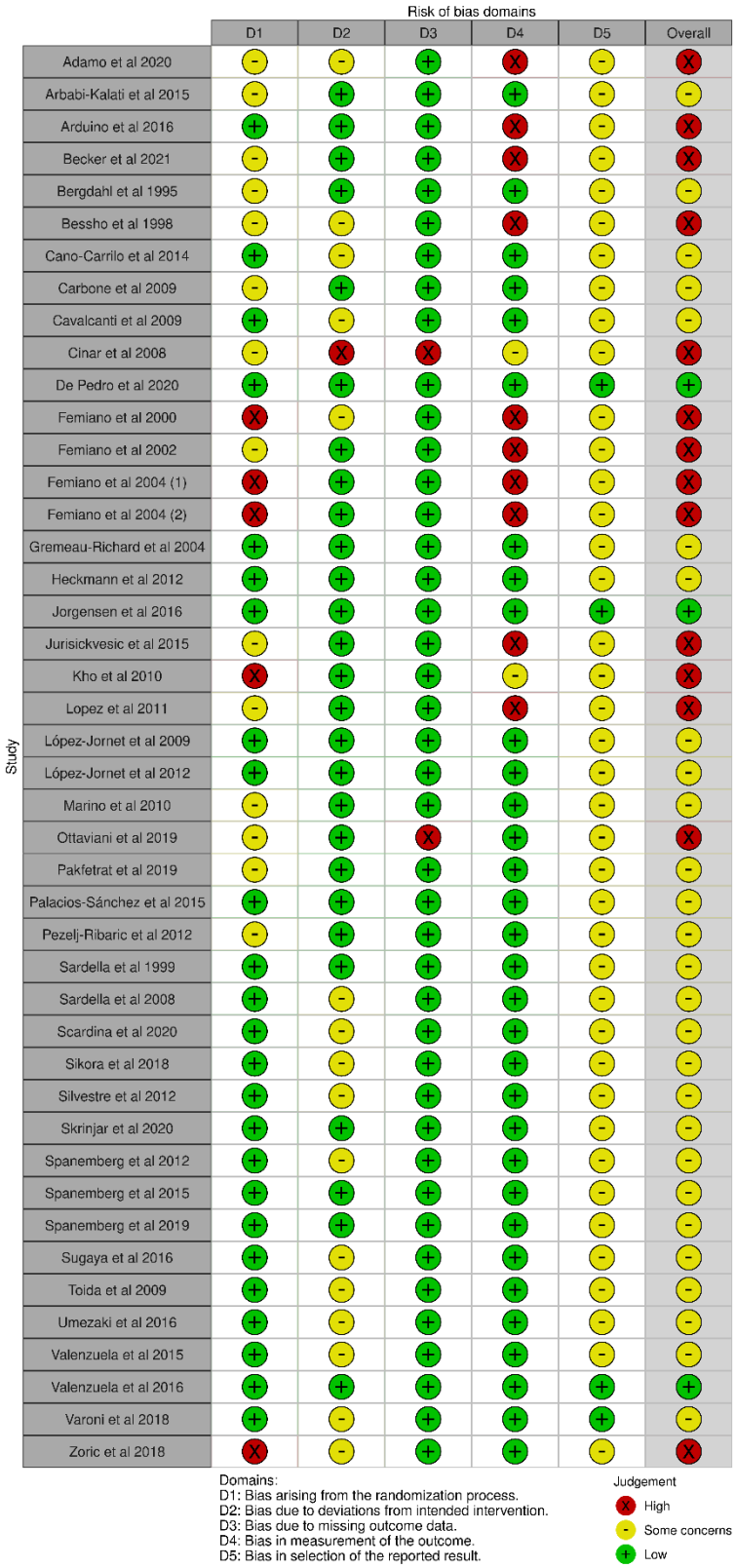
Franco FR, Castro LA, Borsatto MC, Silveira EA, Ribeiro-Rotta RF. 2017. Combined acupuncture and auriculotherapy in burning mouth syndrome treatment: A preliminary single-arm clinical trial. J Altern Complement Med. 23(2):126-134.	Study without a comparison group.
Gambino A, Cabras M, Panagiotakos E, Calvo F, Macciotta A, Cafaro A, Suria M, El Haddad G, Broccoletti R, Arduino PG. 2021. Evaluating the suitability and potential efficiency of cannabis sativa oil for patients with primary burning mouth syndrome: A prospective, open-label, single-arm pilot study. Pain Med. 22(1):142-151	Study without a comparison group.
Garg A, Bhatnagar A, Tayal S, Singh UP. 2017. Merits of oil pulling therapy in the management of xerostomia and stomatopyrosis in burning mouth syndrome. J. Clin. Diagnostic Res. 11(12):ZC27-ZC29.	Study without a comparison group.
Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, Ughetto S, Woda A. 2010. Effect of lingual nerve block on burning mouth syndrome (stomatodynia): A randomized crossover trial. Pain. 149(1):27-32.	Study without a comparison group.
Grushka M, Epstein J, Mott A. 1998. An open-label, dose escalation pilot study of the effect of clonazepam in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 86(5):557-561.	Study without a comparison group.
Hugoson A, Thorstensson B. 1991. Vitamin b status and response to replacement therapy in patients with burning mouth syndrome. Acta Odontol Scand. 49(6):367-375.	Patients with vitamin B1, B2, B6, B12 deficiency.
Kato IT, Pellegrini VD, Prates RA, Ribeiro MS, Wetter NU, Sugaya NN. 2010. Low-level laser therapy in burning mouth syndrome patients: A pilot study. Photomed Laser Surg. 28(6):835-839.	Study without a comparison group.
Kato Y, Sato T, Katagiri A, Umezaki Y, Takenoshita M, Yoshikawa T, Sato Y, Toyofuku A. 2011. Milnacipran dose-effect study in patients with burning mouth syndrome. Clin Neuropharmacol. 34(4):166-169.	Study without a comparison group.

Khan J, Anwer M, Noboru N, Thomas D, Kalladka M. 2019. Topical application in burning mouth syndrome. J Dent Sci. 14(4):352-357.	Observational study.
Ko JY, Kim MJ, Lee SG, Kho HS. 2012. Outcome predictors affecting the efficacy of clonazepam therapy for the management of burning mouth syndrome (bms). Arch Gerontol Geriatr. 55(3):755-761.	Observational study.
Komiyama O, Nishimura H, Makiyama Y, Iida T, Obara R, Shinoda M, Kobayashi M, Noma N, Abe O, De Laat A et al. 2013. Group cognitive-behavioral intervention for patients with burning mouth syndrome. J Oral Sci. 55(1):17-22.	Observational study.
Kuten-Shorrer M, Treister NS, Stock S, Kelley JM, Ji YD, Woo SB, Lerman MA, Palmason S, Sonis ST, Villa A. 2017. Safety and tolerability of topical clonazepam solution for management of oral dysesthesia. Oral Surg Oral Med Oral Pathol Oral Radiol. 124(2):146-151.	Study without a comparison group.
Kuten-Shorrer M, Treister NS, Stock S, Kelley JM, Ji YD, Woo SB, Lerman MA, Palmason S, Sonis ST, Villa A. 2017b. Topical clonazepam solution for the management of burning mouth syndrome: A retrospective study. J. Oral Facial Pain Headache. 31(3):257-263.	Observational study.
López V, Alonso V, Martí N, Calduch L, Jordá E. 2009. Marked response of burning mouth syndrome to pregabalin treatment. Clin Exp Dermatol. 34(7):e449-e450.	Letter to the editor.
Mendizabal M, Laña J, Ginestal E. 2015. Assessment of effectiveness of clonazepam in patients with burning mouth syndrome. Cephalalgia. 35(6):109.	Abstract.
Restivo DA, Lauria G, Marchese-Ragona R, Vigneri R. 2017. Botulinum toxin for burning mouth syndrome. Ann Intern Med. 166(10):762-763.	Letter to the editor.

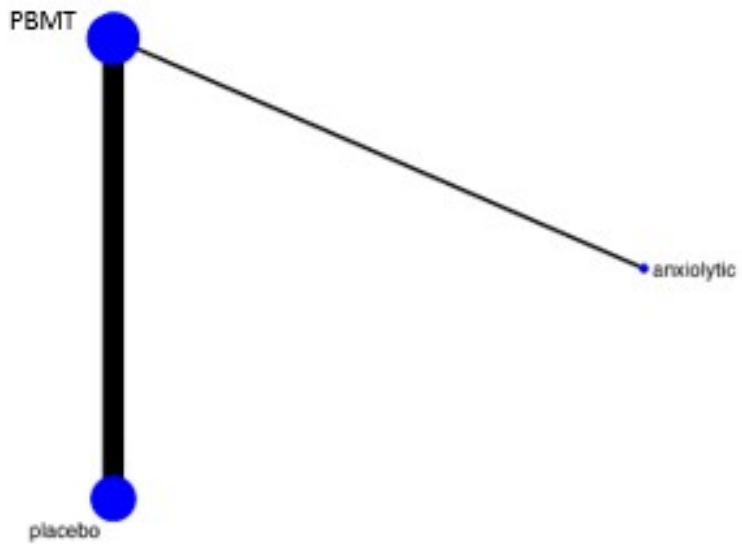
Restivo DA, Vigneri R, Marchese-Ragona R, Pavone A, Lauria G. 2017b. Botulinum toxin for burning mouth syndrome. J. Neurol. Sci. 381:166-167.	Abstract.
Rodríguez-de Rivera-Campillo E, López-López J. 2013. Evaluation of the response to treatment and clinical evolution in patients with burning mouth syndrome. Med Oral Patol Oral. 18(3):e403-e410.	Non-randomized study.
Sardella A, Lodi G, Tarozzi M, Varoni E, Franchini R, Carrassi A. 2013. Acupuncture and burning mouth syndrome: A pilot study. Pain Practice. 13(8):627-632.	Study without a comparison group.
Scardina GA, Ruggieri A, Provenzano F, Messina P. 2010. Burning mouth syndrome: Is acupuncture a therapeutic possibility? Br Dent J. 209(1):E2.	Study without a comparison group.
Steele JC, Bruce AJ, Drage LA, Rogers RS. 2008. Alpha-lipoic acid treatment of 31 patients with sore, burning mouth. Oral Dis. 14(6):529-532.	Observational study.
Suga T, Takenoshita M, Watanabe T, Tu TTH, Mikuzuki L, Hong C, Miura K, Yoshikawa T, Nagamine T, Toyofuku A. 2019. Therapeutic dose of amitriptyline for older patients with burning mouth syndrome. Neuropsychiatr Dis Treat 15:3599-3607. .	Observational study.
Sugimoto K. 2011. The dubious effect of milnacipran for the treatment of burning mouth syndrome. Clin Neuropharmacol. 34(4):170-173.	Study without a comparison group.
Tammials-Salonen T, Forsseii H. 1999. Trazodone in burning mouth pain: A placebo-controlled, double-blind study. J Oral Facial Pain Headache. 13(2):83-88.	Abstract.

Vukoja D, Alajbeg I, Boras VV, Brailo V, Alajbeg IZ, Andabak Rogulj A. 2011. Is effect of low-level laser therapy in patients with burning mouth syndrome result of a placebo? Photomed Laser Surg. 29(9):647-648.	Letter to the editor.
Woda A, Navez ML, Picard P, Gremeau C, Pichard-Le, ri E. 1998. A possible therapeutic solution for stomatodynia (burning mouth syndrome). J Orofac Pain. 12(4):272-278.	Observational study.
Yang HW, Huang YF. 2011. Treatment of burning mouth syndrome with a low-level energy diode laser. Photomed Laser Surg 29(2):123-125.	Study without a comparison group.

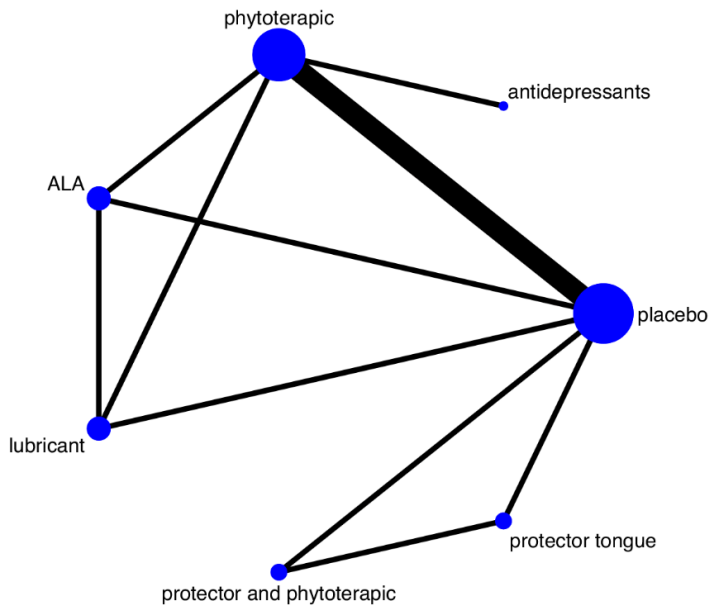
Appendix Figure 1. Risk of bias of 44 randomized controlled trials (RCTs). Red represents high risk of bias; yellow represents some concerns; and green represents low risk of bias.



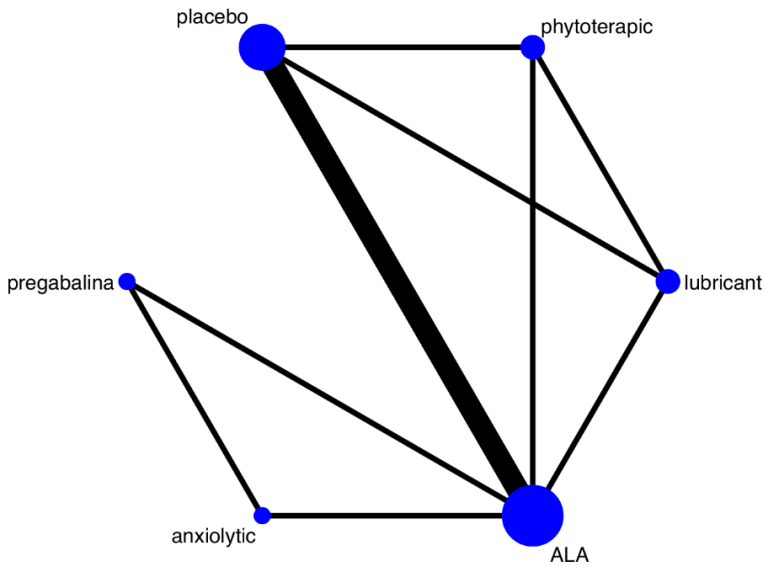
Appendix Geometry 1. Network geometry for pain - photobiomodulation therapy (PBMT).



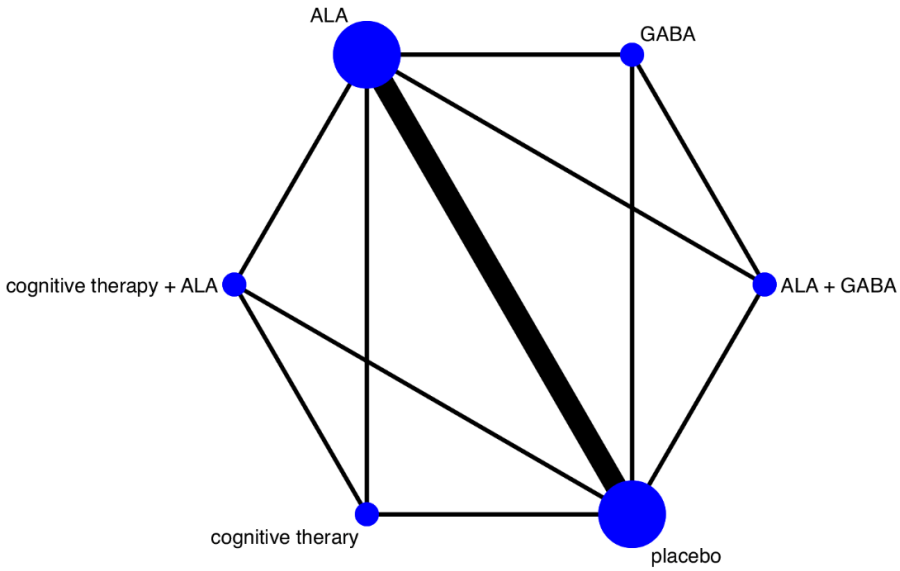
Appendix Geometry 2. Network geometry for pain - phytotherapics.



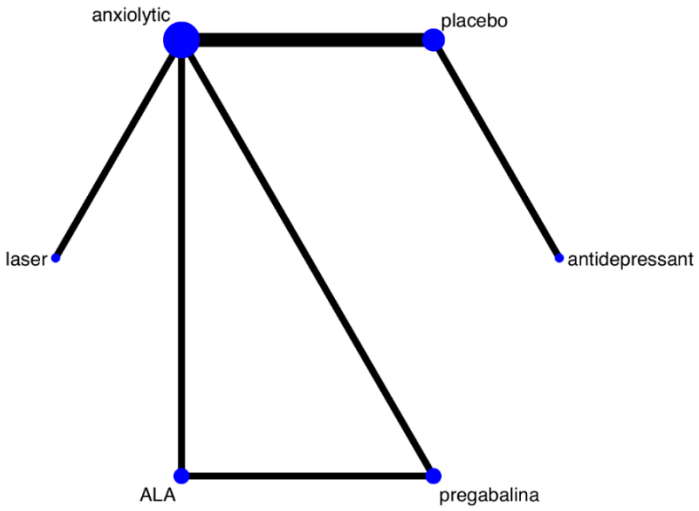
Appendix Geometry 3. Network geometry for pain (continuous outcome) - alpha-lipoic acid (ALA).



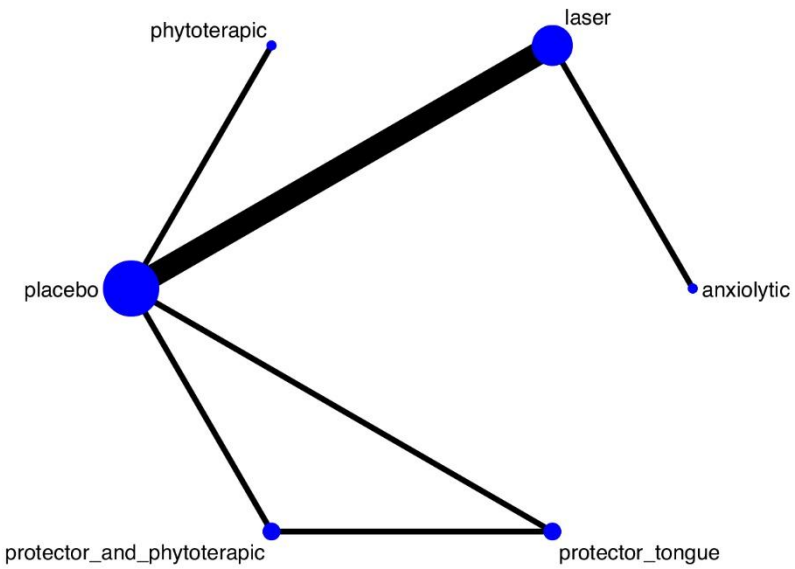
Appendix Geometry 4. Network geometry for pain (binary outcome) - alpha-lipoic acid (ALA).



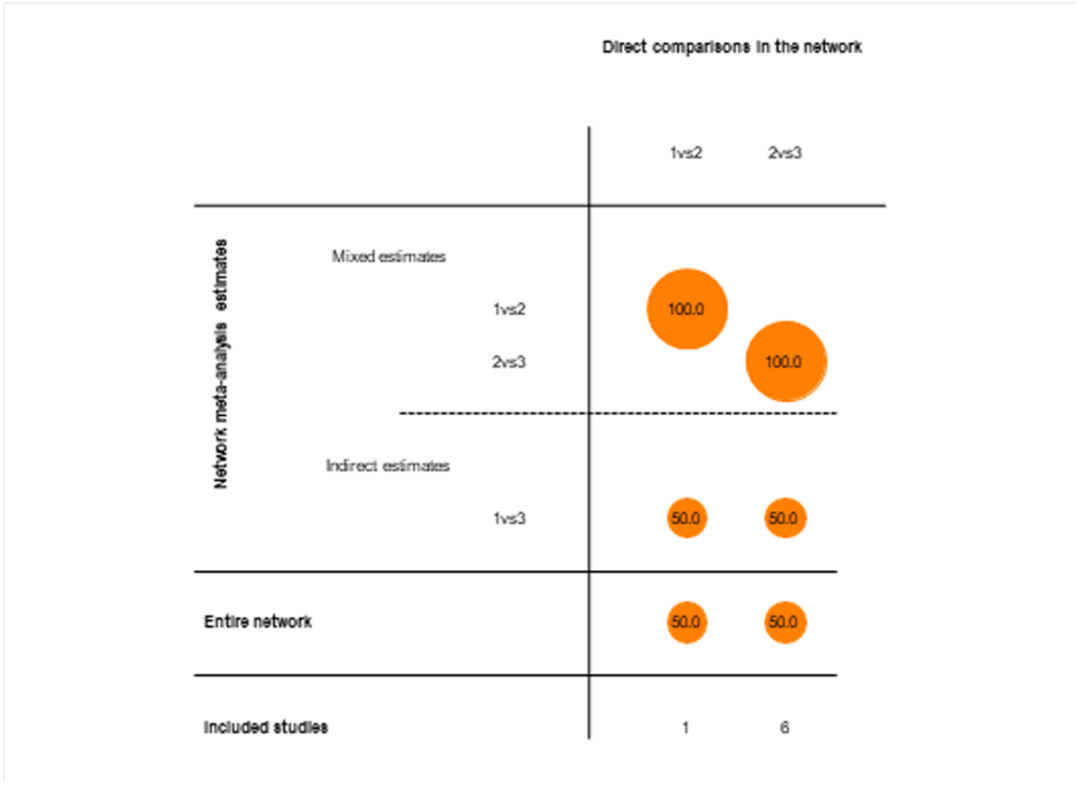
Appendix Geometry 5. Network geometry for pain - anxiolytic and antidepressive.



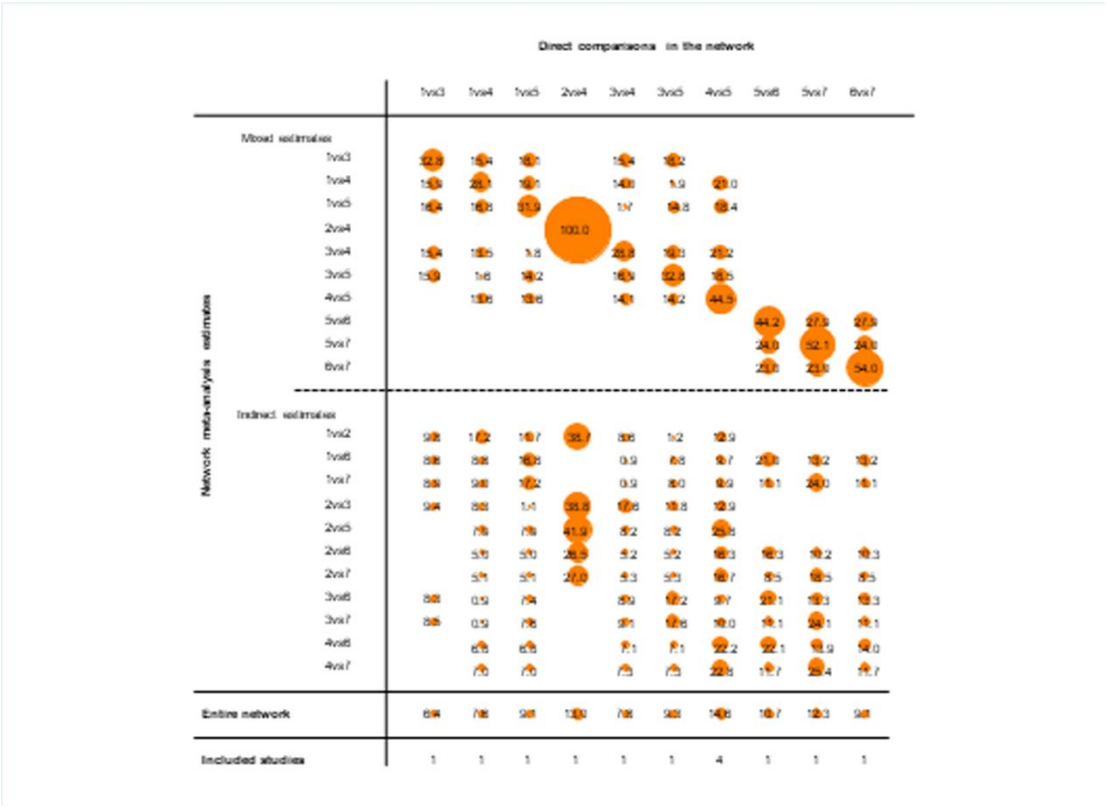
Appendix Geometry 6. Network geometry for quality of life – all treatments.



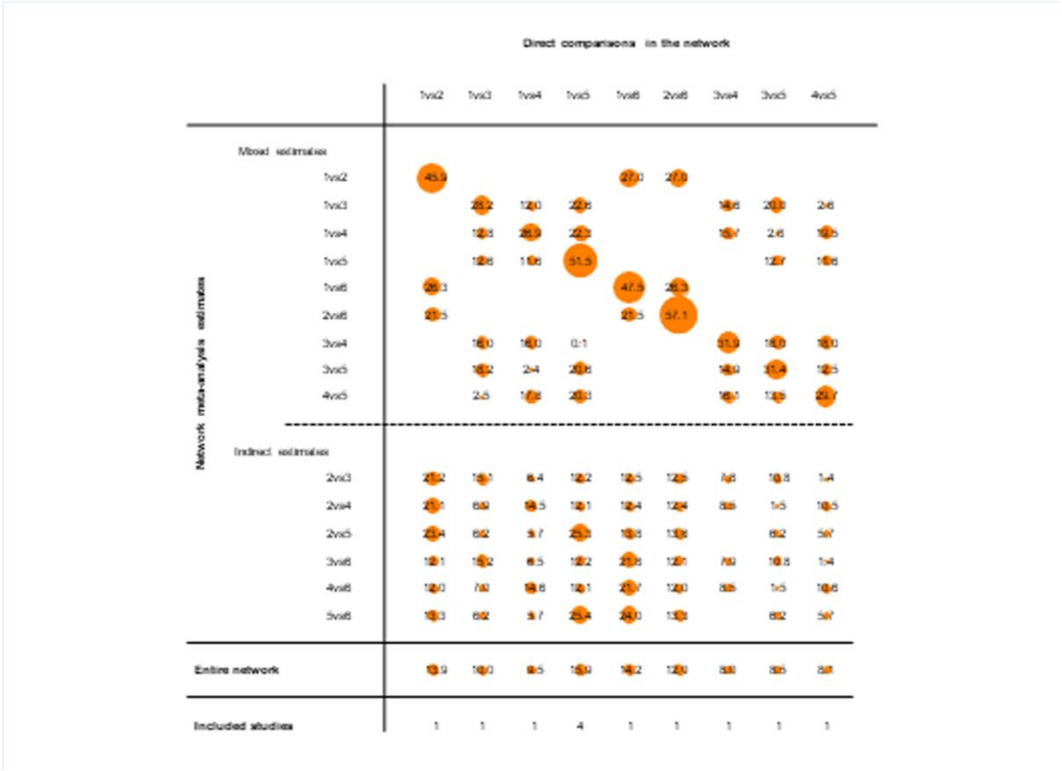
Appendix Plot 1. Contribution plot for photobiomodulation therapy (PBMT). 1: anxiolytic; 2: PBMT; 3: placebo (reference).



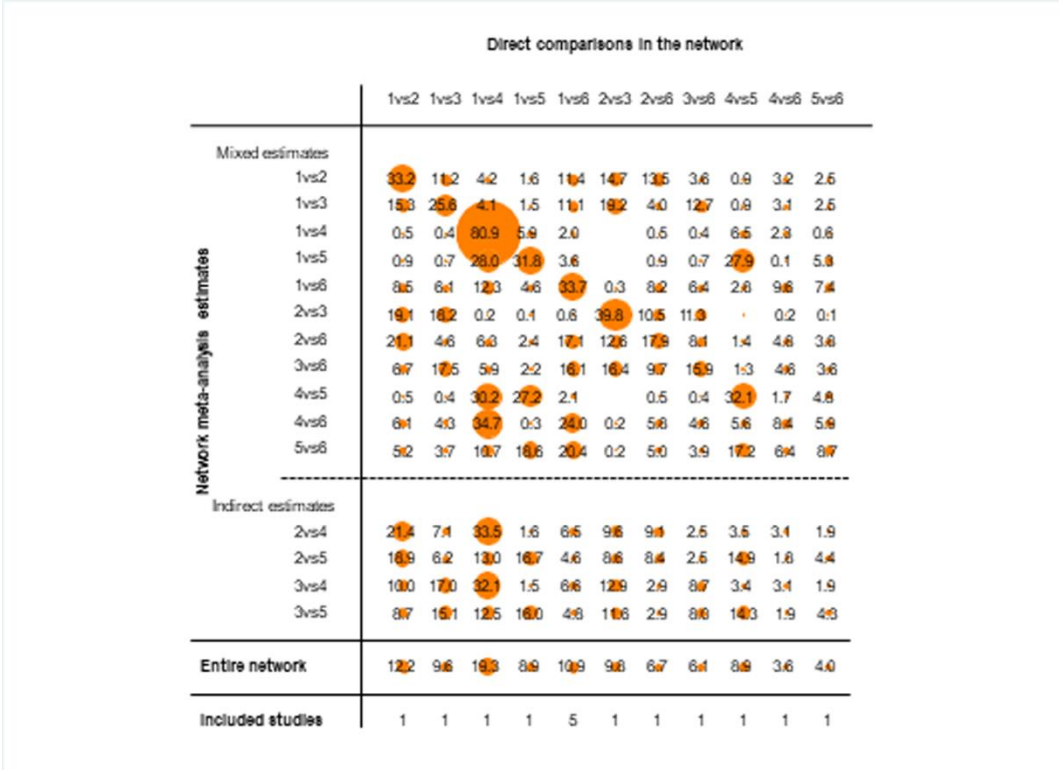
Appendix Plot 2. Contribution plot for phytotherapic. 1: ALA (alpha-lipoic acid); 2: antidepressants; 3: lubricant; 4: phytotherapic; 5: placebo (reference); 6: tongue protector + phytotherapic; 7: tongue protector.



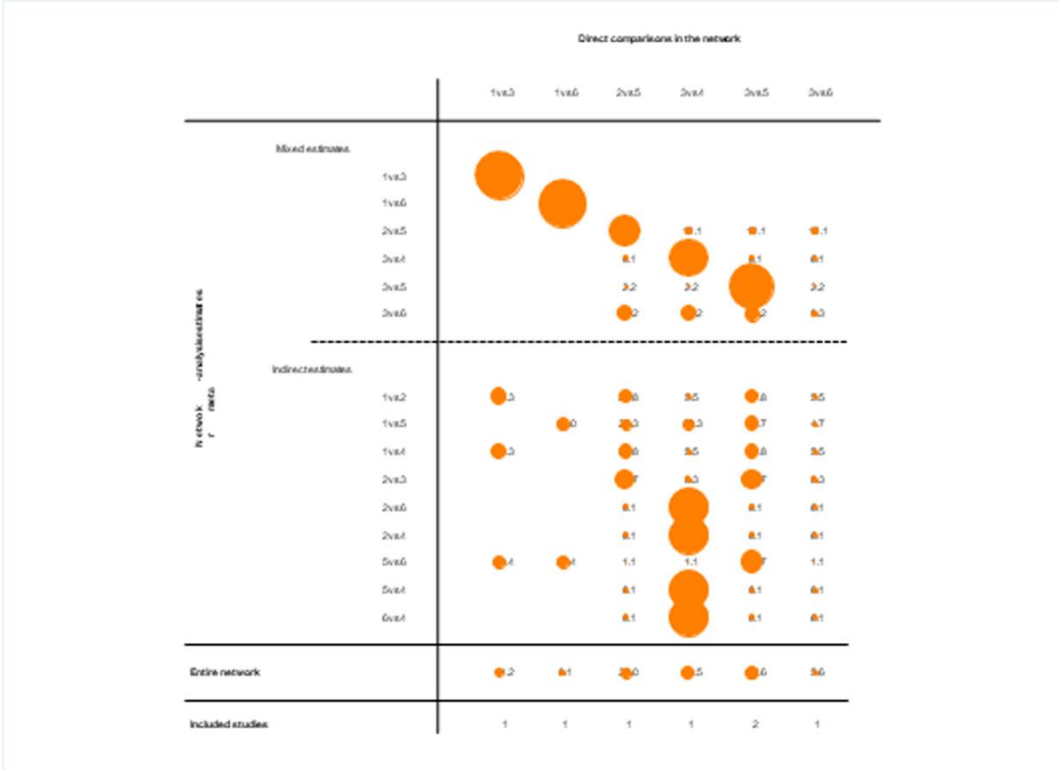
Appendix Plot 3. Contribution plot for alpha-lipoic acid (ALA), continuous outcome. 1: ALA; 2: anxiolytic; 3: lubricant; 4: phytotherapic; 5: placebo (reference); 6: gabapentin (GABA).



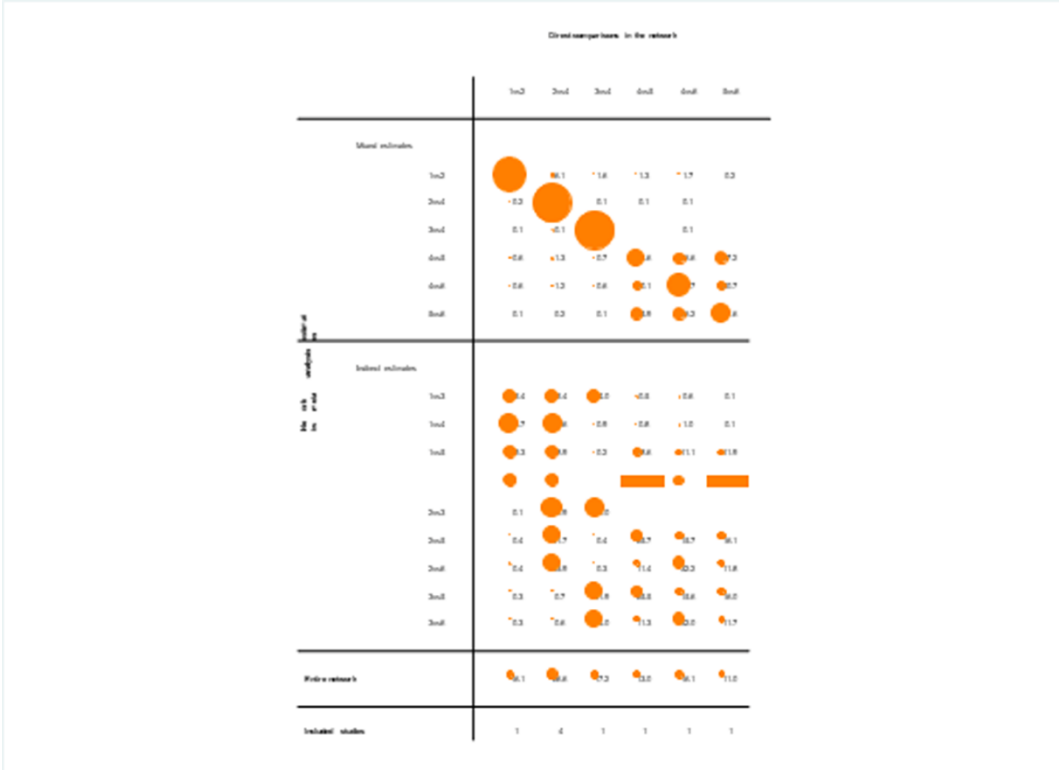
Appendix Plot 4. Contribution plot for alpha-lipoic acid (ALA), binary outcome. 1: ALA; 2: ALA + gabapentin (GABA); 3: GABA; 4: cognitive therapy + ALA; 5: cognitive therapy; 6: placebo (reference).



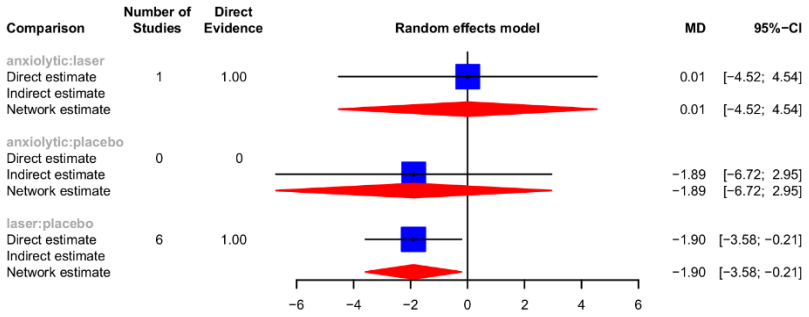
Appendix Plot 5. Contribution plot for anxiolytic/ antidepressant. 1: ALA; 2: antidepressant; 3: anxiolytic; 4: photobiomodulation therapy (PBMT); 5: placebo (reference); 6: gabapentin (GABA).



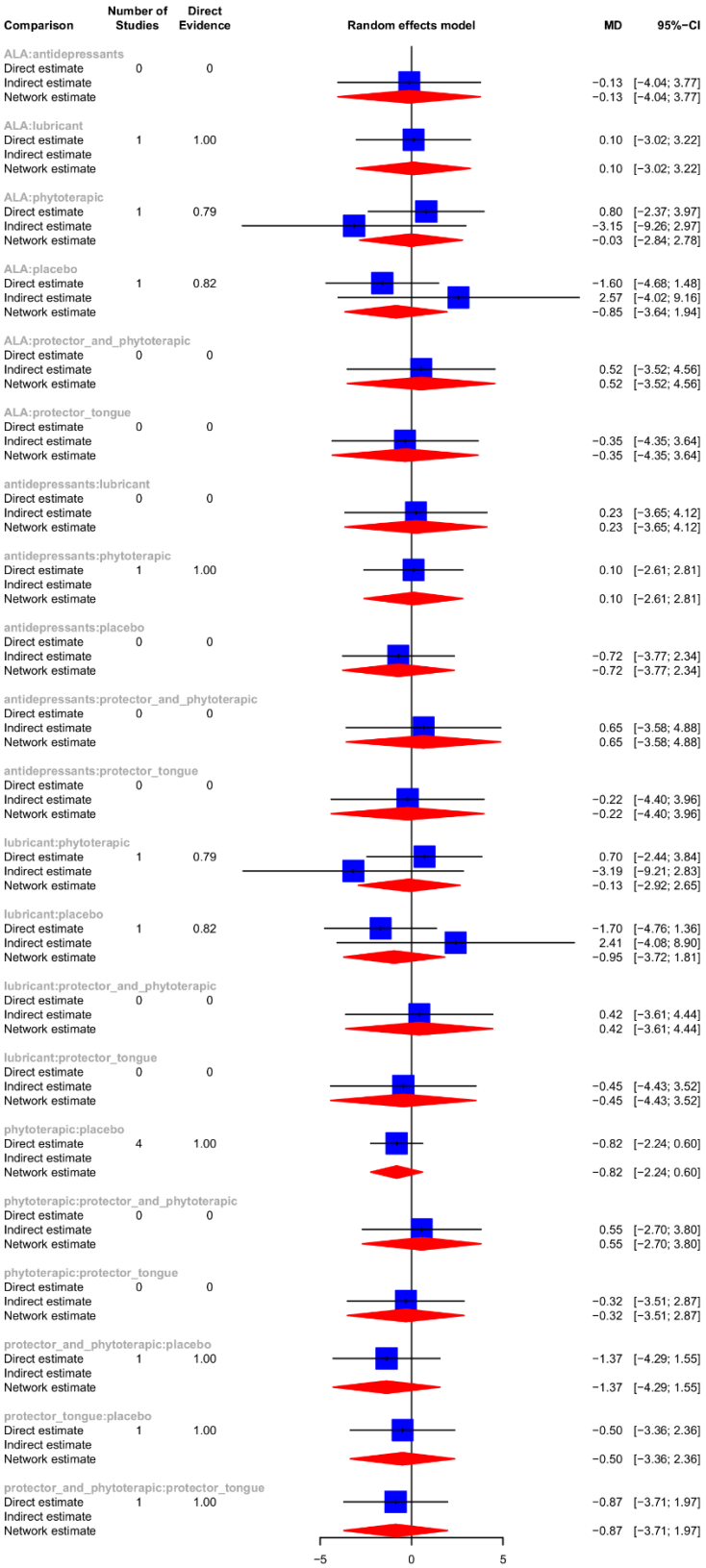
Appendix Plot 6. Contribution plot for quality of life. 1: anxiolytic; 2: photobiomodulation therapy (PBMT); 3: phytotherapic; 4: placebo (reference); 6: tongue protector + phytotherapic; 7: tongue protector.



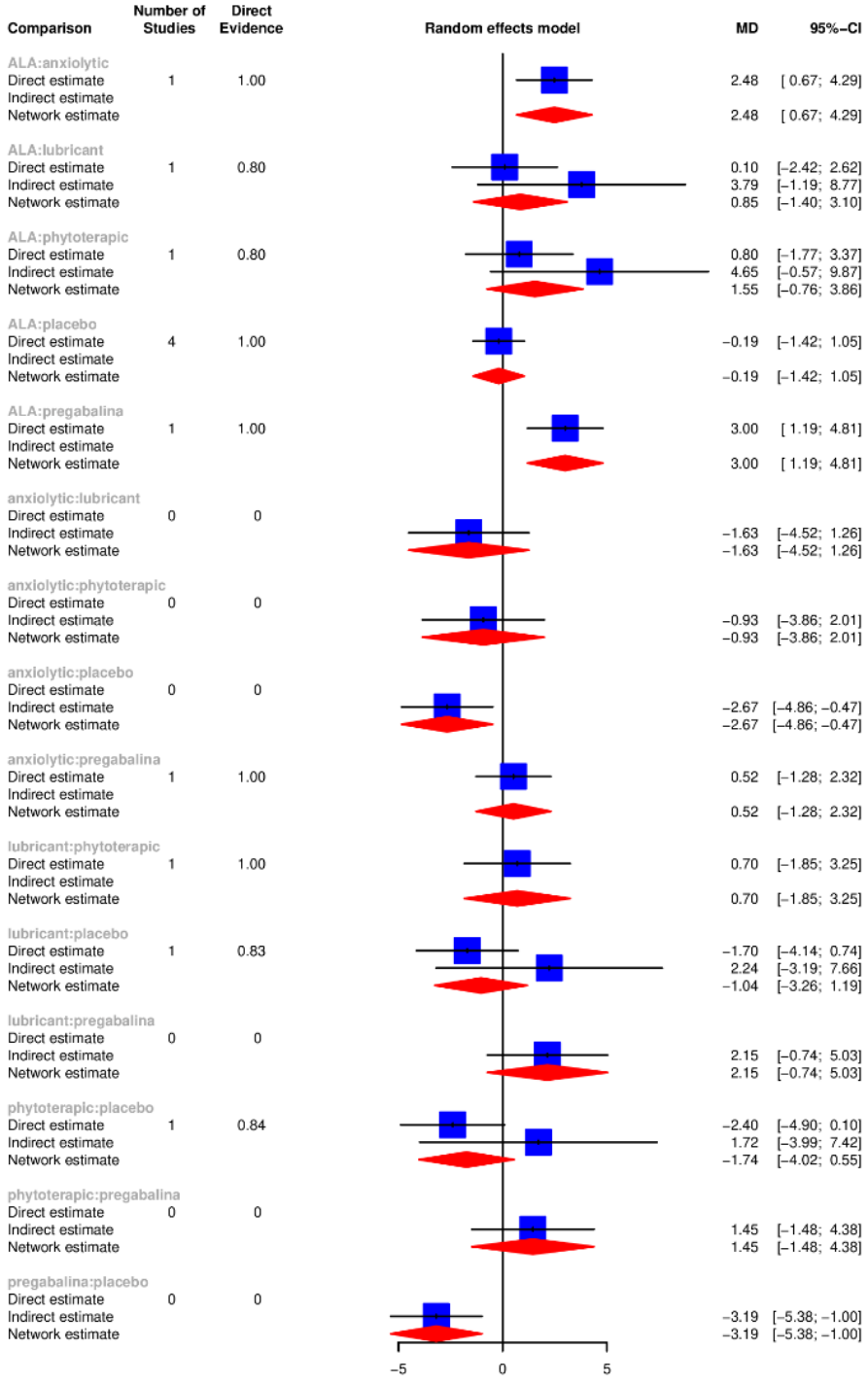
Appendix Figure 2: Direct, indirect and network estimates for pain – photobiomodulation therapy (PBMT -laser), random effect model.



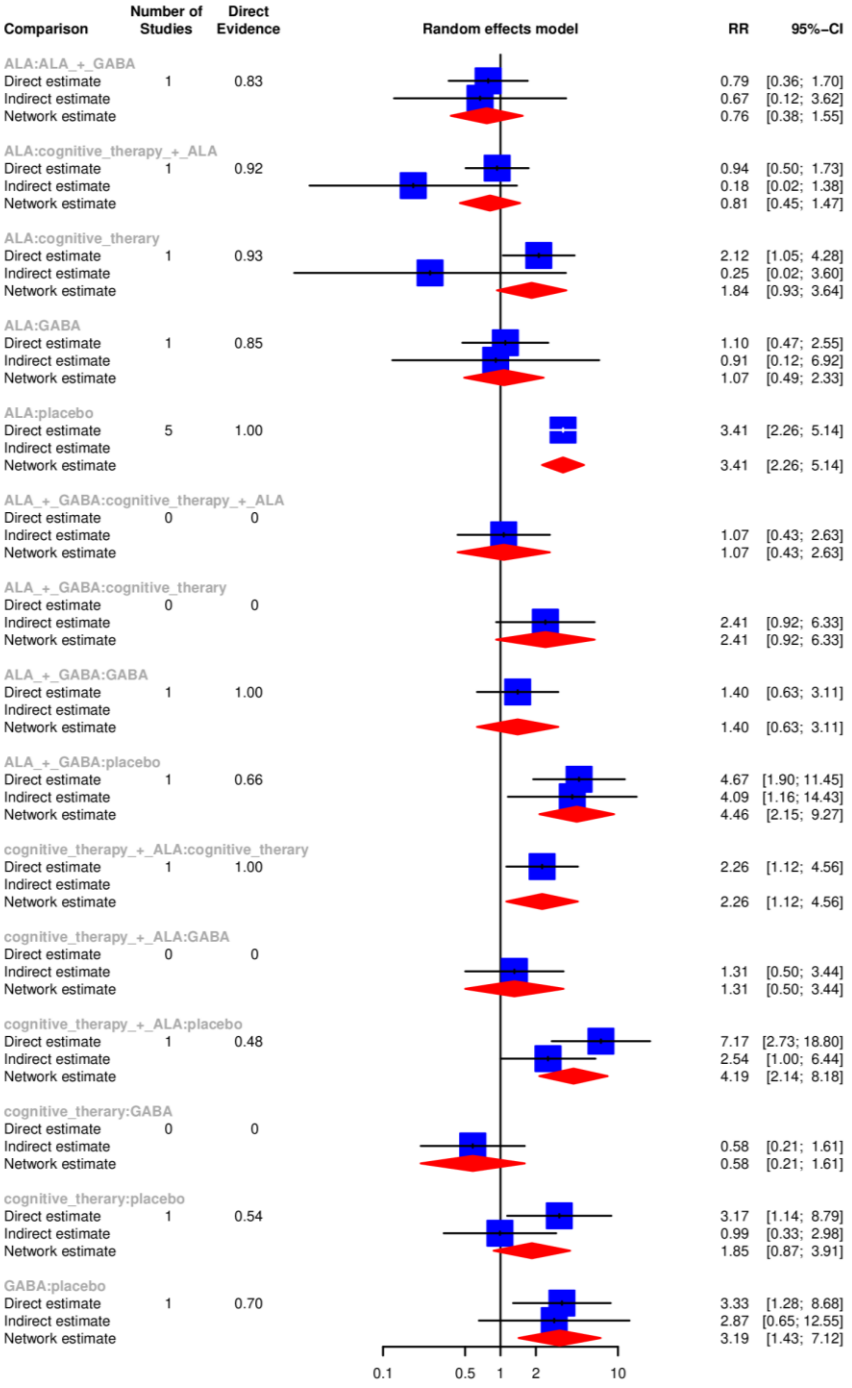
Appendix Figure 3: Direct, indirect and network estimates for pain – phytotherapics, random effect model.



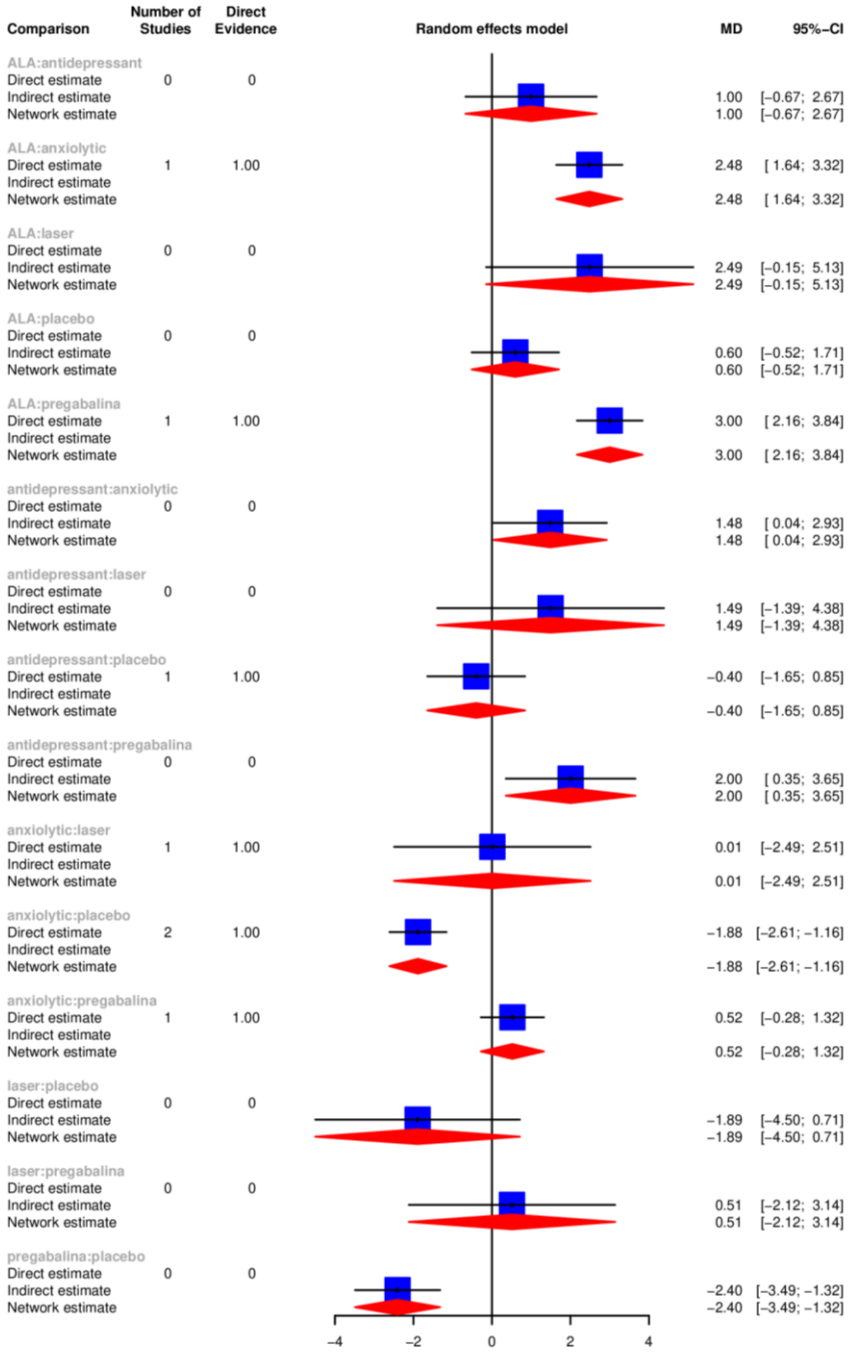
Appendix Figure 4: Direct, indirect and network estimates for pain (continuous outcome) – alpha-lipoic acid (ALA), random effect model.



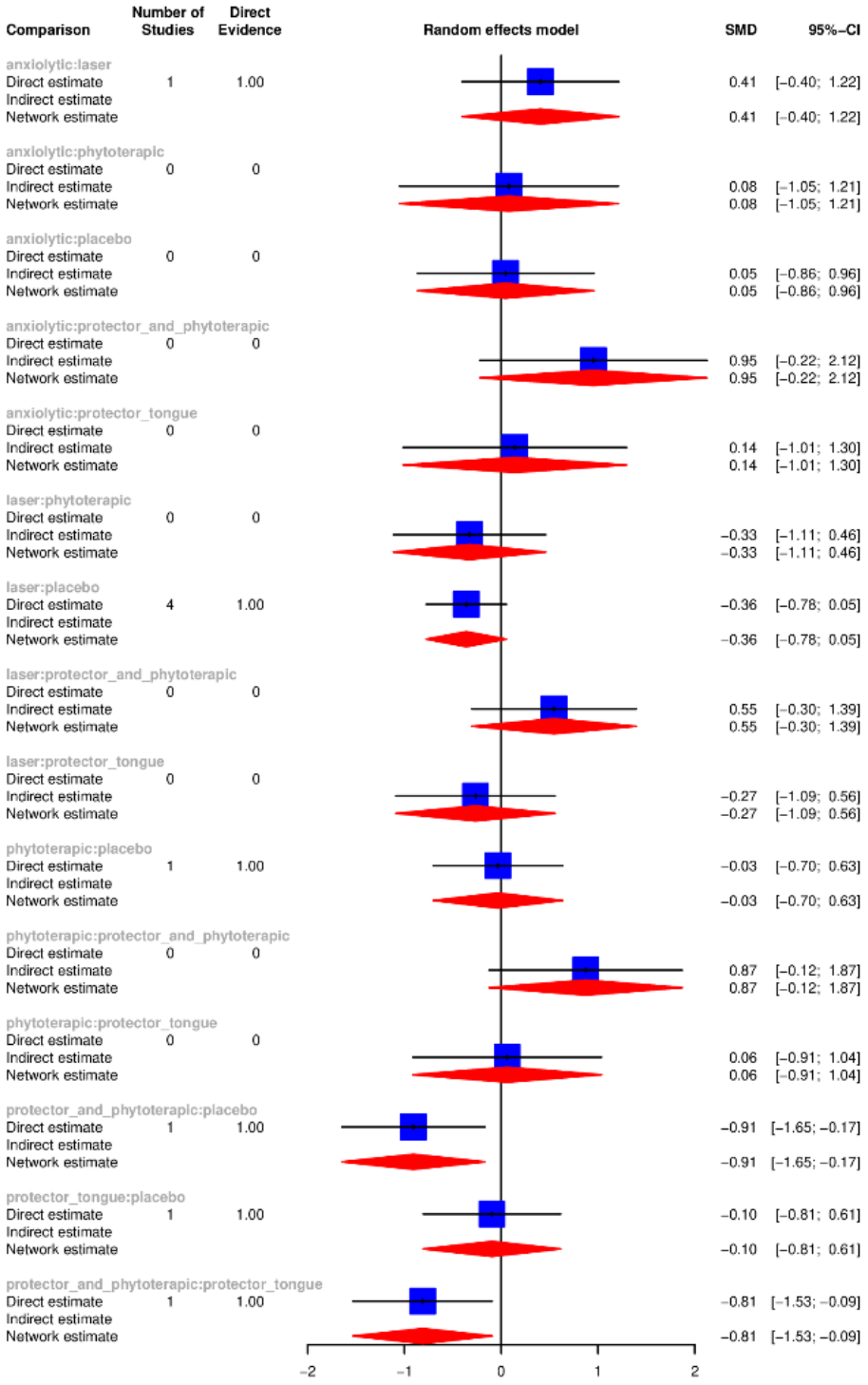
Appendix Figure 5: Direct, indirect and network estimates for pain (binary outcome) – alpha-lipoic acid (ALA), random effect model.



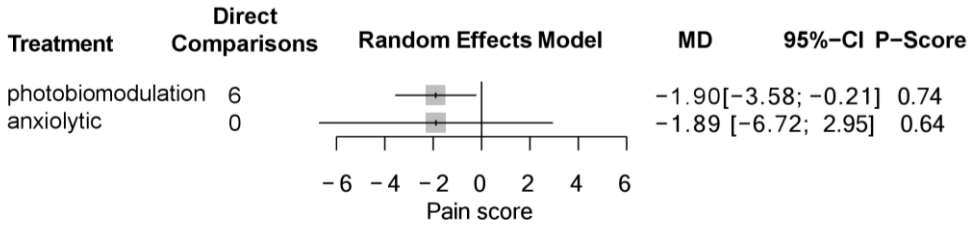
Appendix Figure 6: Direct, indirect and network estimates for pain - anxiolytic and antidepressive, random effect model.



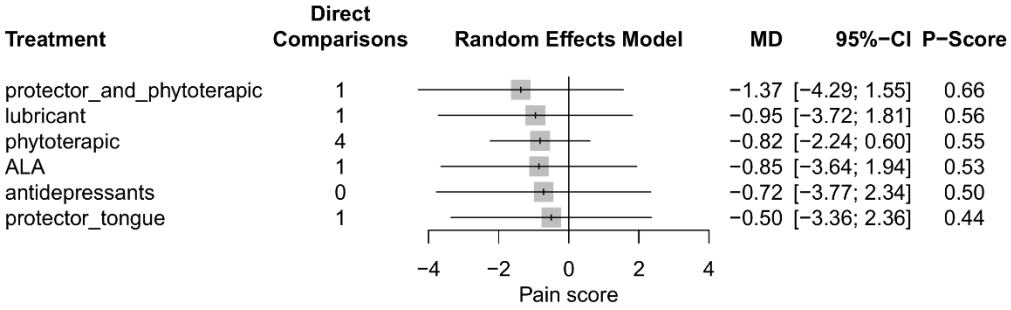
Appendix Figure 7: Direct, indirect and network estimates for quality of life – all treatments, random effect model.



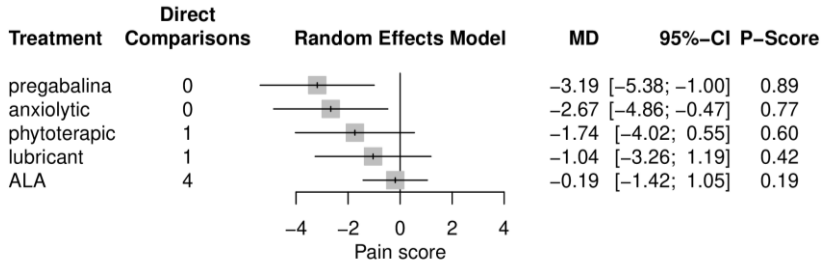
Appendix Figure 8: Network estimates for pain – photobiomodulation therapy (PBMT), random effect model.



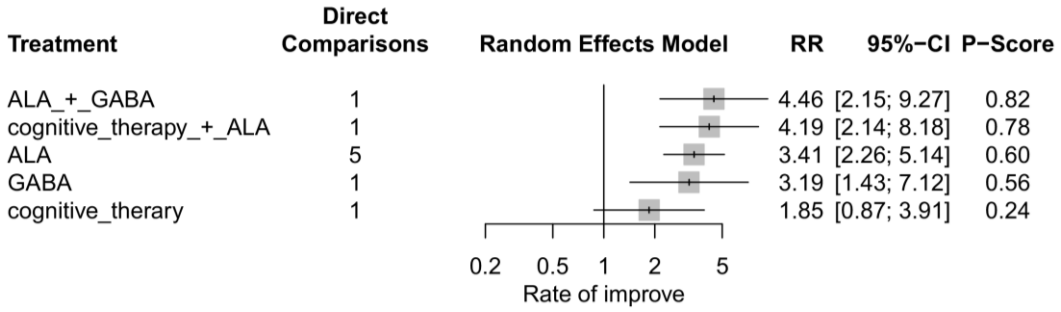
Appendix Figure 9: Network estimates for pain – phytotherapics, random effect model.



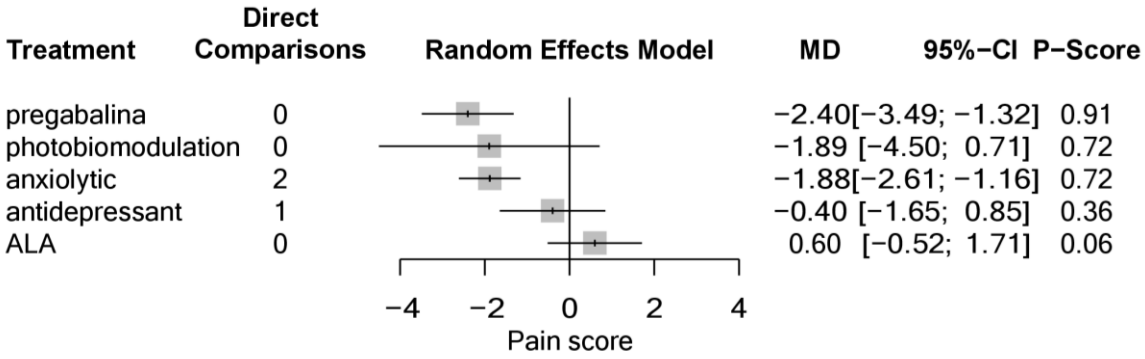
Appendix Figure 10: Network estimates for pain – alpha-lipoic acid (continuous outcome), random effect model.



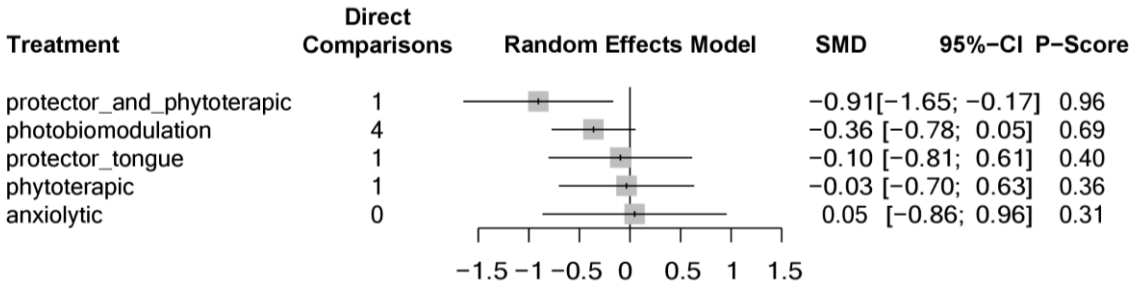
Appendix Figure 11: Network estimates for pain – alpha-lipoic acid (binary outcome), random effect model.



Appendix Figure 12: Network estimates for pain – anxiolytic and antidepressives, random effect model.



Appendix Figure 13: Network estimates for quality of life, random effect model.



League Table 1a.

anxiolytic	**0.01 (-2.40 - 2.42)**	**.**
0.01 (-2.40 - 2.42)	**PBMT**	**-1.41 (-1.93 - -0.88)**
-1.40 (-3.86 - 1.07)	**-1.41 (-1.93 - -0.88)**	**placebo**
League table for pain (consistency fixed-effects model adjusted for follow-up)		

Pain for photobiomodulation therapy (PBMT), fixed effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% CI. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 1b.

anxiolytic	0.01 (-4.52 - 4.54)	**.**
0.01 (-4.52 - 4.54)	**PBMT**	-1.90 (-3.58 - -0.21)
-1.89 (-6.72 - 2.95)	-1.90 (-3.58 - -0.21)	**placebo**
League table for pain (consistency random-effects model adjusted for follow-up)		

Pain for photobiomodulation therapy (PBMT), random- effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% CI. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 2a.

ALA	.	0.10 (-1.72 - 1.92)	0.80 (-1.09 - 2.69)	-1.60 (-3.34 - 0.14)	.	.
-0.50 (-2.36 - 1.37)	**antidepressants**	.	0.10 (-0.84 - 1.04)	.	.	.
0.10 (-1.72 - 1.92)	0.60 (-1.23 - 2.42)	**lubricant**	0.70 (-1.15 - 2.55)	-1.70 (-3.41 - 0.01)	.	.
-0.40 (-2.01 - 1.22)	0.10 (-0.84 - 1.04)	-0.50 (-2.07 - 1.07)	**phytotherapic**	-0.35 (-0.92 - 0.23)	.	.
-0.74 (-2.34 - 0.85)	-0.25 (-1.34 - 0.85)	-0.84 (-2.40 - 0.71)	-0.35 (-0.92 - 0.23)	**placebo**	1.37 (-0.08 - 2.82)	0.50 (-0.81 - 1.81)
0.63 (-1.53 - 2.78)	1.12 (-0.69 - 2.94)	0.53 (-1.59 - 2.65)	1.02 (-0.53 - 2.58)	1.37 (-0.08 - 2.82)	**protector + phytotherapic**	-0.87 (-2.14 - 0.40)
-0.24 (-2.30 - 1.82)	0.25 (-1.45 - 1.96)	-0.34 (-2.37 - 1.69)	0.15 (-1.27 - 1.58)	0.50 (-0.81 - 1.81)	-0.87 (-2.14 - 0.40)	**tongue protector**
League table for pain (consistency fixed-effects model adjusted for follow-up)						

Pain for phytotherapics, fixed effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 2b.

ALA	**.**	0.10 (-3.02 - 3.22)	0.80 (-2.37 - 3.97)	-1.60 (-4.68 - 1.48)	**.**	**.**
-0.13 (-4.04 - 3.77)	**antidepressants**	.	0.10 (-2.61 - 2.81)	.	.	.
0.10 (-3.02 - 3.22)	0.23 (-3.65 - 4.12)	**lubricant**	0.70 (-2.44 - 3.84)	-1.70 (-4.76 - 1.36)	.	.
-0.03 (-2.84 - 2.78)	0.10 (-2.61 - 2.81)	-0.13 (-2.92 - 2.65)	**phytotherapic**	-0.82 (-2.24 - 0.60)	.	.
-0.85 (-3.64 - 1.94)	-0.72 (-3.77 - 2.34)	-0.95 (-3.72 - 1.81)	-0.82 (-2.24 - 0.60)	**placebo**	1.37 (-1.55 - 4.29)	0.50 (-2.36 - 3.36)
0.52 (-3.52 - 4.56)	0.65 (-3.58 - 4.88)	0.42 (-3.61 - 4.44)	0.55 (-2.70 - 3.80)	1.37 (-1.55 - 4.29)	**protector + phytotherapic**	-0.87 (-3.71 - 1.97)
-0.35 (-4.35 - 3.64)	-0.22 (-4.40 - 3.96)	-0.45 (-4.43 - 3.52)	-0.32 (-3.51 - 2.87)	0.50 (-2.36 - 3.36)	-0.87 (-3.71 - 1.97)	**protector tongue**
League table for pain (consistency random-effects model adjusted for follow-up)						

Pain for phytotherapics, random effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 3a.

ALA	2.48 (1.99 - 2.97)	0.10 (-1.72 - 1.92)	0.80 (-1.09 - 2.69)	-0.16 (-1.04 - 0.71)	3.00 (2.52 - 3.48)
2.48 (1.99 - 2.97)	**anxiolytic**	.	.	.	0.52 (0.10 - 0.94)
0.91 (-0.69 - 2.51)	-1.57 (-3.25 - 0.11)	**lubricant**	0.70 (-1.15 - 2.55)	-1.70 (-3.41 - 0.01)	.
1.61 (-0.08 - 3.30)	-0.87 (-2.63 - 0.89)	0.70 (-1.15 - 2.55)	**phytotherapic**	-2.40 (-4.18 - -0.62)	.
-0.16 (-1.04 - 0.71)	-2.64 (-3.65 - -1.64)	-1.07 (-2.65 - 0.50)	-1.77 (-3.43 - -0.12)	**placebo**	.
3.00 (2.52 - 3.48)	0.52 (0.10 - 0.94)	2.09 (0.42 - 3.77)	1.39 (-0.36 - 3.15)	3.16 (2.17 - 4.16)	**pregabalin**
League table for pain (consistency fixed-effects model adjusted for follow-up)					

Pain for alpha-acid lipoic (ALA, continuous outcome), fixed effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 3b.

ALA	2.48 (0.67 - 4.29)	0.10 (-2.42 - 2.62)	0.80 (-1.77 - 3.37)	-0.19 (-1.42 - 1.05)	3.00 (1.19 - 4.81)
2.48 (0.67 - 4.29)	**anxiolytic**	.	.	.	0.52 (-1.28 - 2.32)
0.85 (-1.40 - 3.10)	-1.63 (-4.52 - 1.26)	**lubricant**	0.70 (-1.85 - 3.25)	-1.70 (-4.14 - 0.74)	.
1.55 (-0.76 - 3.86)	-0.93 (-3.86 - 2.01)	0.70 (-1.85 - 3.25)	**phytotherapic**	-2.40 (-4.90 - 0.10)	.
-0.19 (-1.42 - 1.05)	-2.67 (-4.86 - -0.47)	-1.04 (-3.26 - 1.19)	-1.74 (-4.02 - 0.55)	**placebo**	.
3.00 (1.19 - 4.81)	0.52 (-1.28 - 2.32)	2.15 (-0.74 - 5.03)	1.45 (-1.48 - 4.38)	3.19 (1.00 - 5.38)	**pregabalin**
League table for pain (consistency random-effects model adjusted for follow-up)					

Pain for alpha-acid lipoic (ALA, continuous outcome), random effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 4a.

ALA	0.79 (0.48 - 1.28)	0.94 (0.81 - 1.08)	2.12 (1.47 - 3.05)	1.10 (0.61 - 1.99)	3.15 (2.36 - 4.21)
0.75 (0.48 - 1.17)	**ALA + GABA**	**.**	**.**	1.40 (0.83 - 2.36)	4.67 (2.39 - 9.09)
0.92 (0.80 - 1.06)	1.23 (0.77 - 1.96)	**cognitive therapy+ ALA**	2.26 (1.57 - 3.25)	**.**	7.17 (3.37 - 15.24)
2.09 (1.45 - 3.01)	2.78 (1.56 - 4.94)	2.26 (1.57 - 3.25)	**cognitive therary**	**.**	3.17 (1.39 - 7.23)
1.05 (0.60 - 1.83)	1.40 (0.83 - 2.36)	1.14 (0.64 - 2.02)	0.50 (0.26 - 0.98)	**GABA**	3.33 (1.58 - 7.02)
3.15 (2.36 - 4.21)	4.20 (2.59 - 6.81)	3.42 (2.49 - 4.70)	1.51 (0.95 - 2.40)	3.00 (1.67 - 5.39)	**placebo**
League table for pain (consistency fixed-effects model adjusted for follow-up)					

Pain for alfa-acid lipoic (ALA, binary outcome), fixed effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 4b.

ALA	0.79 (0.36 - 1.70)	0.94 (0.50 - 1.73)	2.12 (1.05 - 4.28)	1.10 (0.47 - 2.55)	3.41 (2.26 - 5.14)
0.76 (0.38 - 1.55)	**ALA + GABA**	.	.	1.40 (0.63 - 3.11)	4.67 (1.90 - 11.45)
0.81 (0.45 - 1.47)	1.07 (0.43 - 2.63)	**cognitive therapy+ ALA**	2.26 (1.12 - 4.56)	.	7.17 (2.73 - 18.80)
1.84 (0.93 - 3.64)	2.41 (0.92 - 6.33)	2.26 (1.12 - 4.56)	**cognitive therapy**	.	3.17 (1.14 - 8.79)
1.07 (0.49 - 2.33)	1.40 (0.63 - 3.11)	1.31 (0.50 - 3.44)	0.58 (0.21 - 1.61)	**GABA**	3.33 (1.28 - 8.68)
3.41 (2.26 - 5.14)	4.46 (2.15 - 9.27)	4.19 (2.14 - 8.18)	1.85 (0.87 - 3.91)	3.19 (1.43 - 7.12)	**placebo**
League table for pain (consistency random-effects model adjusted for follow-up)					

Pain for alfa-acid lipoic (ALA, binary outcome), random effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 5a.

ALA	.	2.48 (1.99 - 2.97)	.	.	3.00 (2.52 - 3.48)
0.91 (-0.29 - 2.10)	**antidepressant**	.	.	-0.40 (-1.44 - 0.64)	.
2.48 (1.99 - 2.97)	1.57 (0.48 - 2.67)	**anxiolytic**	0.01 (-2.40 - 2.42)	-1.97 (-2.31 - -1.64)	0.52 (0.10 - 0.94)
2.49 (0.03 - 4.95)	1.58 (-1.06 - 4.23)	0.01 (-2.40 - 2.42)	**PBMT**	.	.
0.51 (-0.09 - 1.10)	-0.40 (-1.44 - 0.64)	-1.97 (-2.31 - -1.64)	-1.98 (-4.41 - 0.45)	**placebo**	.
3.00 (2.52 - 3.48)	2.09 (0.92 - 3.26)	0.52 (0.10 - 0.94)	0.51 (-1.93 - 2.95)	2.49 (1.96 - 3.03)	**pregabalin**
League table for pain (consistency fixed-effects model adjusted for follow-up)					

Pain for anxiolytic and antidepressant, fixed effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 5b.

ALA	.	2.48 (1.64 - 3.32)	.	.	3.00 (2.16 - 3.84)
1.00 (-0.67 - 2.67)	**antidepressant**	.	.	-0.40 (-1.65 - 0.85)	.
2.48 (1.64 - 3.32)	1.48 (0.04 - 2.93)	**anxiolytic**	0.01 (-2.49 - 2.51)	-1.88 (-2.61 - -1.16)	0.52 (-0.28 - 1.32)
2.49 (-0.15 - 5.13)	1.49 (-1.39 - 4.38)	0.01 (-2.49 - 2.51)	**PBMT**	.	.
0.60 (-0.52 - 1.71)	-0.40 (-1.65 - 0.85)	-1.88 (-2.61 - -1.16)	-1.89 (-4.50 - 0.71)	**placebo**	.
3.00 (2.16 - 3.84)	2.00 (0.35 - 3.65)	0.52 (-0.28 - 1.32)	0.51 (-2.12 - 3.14)	2.40 (1.32 - 3.49)	**pregabalin**
League table for pain (consistency random-effects model adjusted for follow-up)					

Pain for anxiolytic and antidepressant, random effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Pain presents MD with 95% Cl. Positive MD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative MD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 6a.

anxiolytic	0.41 (-0.29 - 1.10)	.	.	.	.
0.41 (-0.29 - 1.10)	**PBMT**	.	-0.33 (-0.67 - 0.02)	.	.
0.11 (-0.82 - 1.05)	-0.29 (-0.92 - 0.33)	**phytotherapics**	-0.03 (-0.56 - 0.49)	.	.
0.08 (-0.70 - 0.85)	-0.33 (-0.67 - 0.02)	-0.03 (-0.56 - 0.49)	**placebo**	0.91 (0.30 - 1.52)	0.10 (-0.48 - 0.67)
0.99 (0.00 - 1.97)	0.58 (-0.12 - 1.28)	0.87 (0.07 - 1.68)	0.91 (0.30 - 1.52)	**protector** + phytoterapic	-0.81 (-1.40 - -0.23)
0.17 (-0.79 - 1.14)	-0.23 (-0.90 - 0.44)	0.06 (-0.71 - 0.84)	0.10 (-0.48 - 0.67)	-0.81 (-1.40 - -0.23)	**tongue protector**
League table for quality of life (consistency fixed-effects model adjusted for follow-up)					

Quality of life for all treatments, fixed effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Quality of life presents SMD with 95% Cl. Positive SMD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative SMD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

League Table 6b.

anxiolytic	0.41 (-0.40 - 1.22**)**	**.**	**.**	**.**	**.**
0.41 (-0.40 - 1.22)	**PBMT**	.	-0.36 (-0.78 - 0.05)	.	.
0.08 (-1.05 - 1.21)	-0.33 (-1.11 - 0.46)	**phytotherapic**	-0.03 (-0.70 - 0.63)	.	.
0.05 (-0.86 - 0.96)	-0.36 (-0.78 - 0.05)	-0.03 (-0.70 - 0.63)	**placebo**	0.91 (0.17 - 1.65)	0.10 (-0.61 - 0.81)
0.95 (-0.22 - 2.12)	0.55 (-0.30 - 1.39)	0.87 (-0.12 - 1.87)	0.91 (0.17 - 1.65)	**protector + phytoterapic**	-0.81 (-1.53 - -0.09)
0.14 (-1.01 - 1.30)	-0.27 (-1.09 - 0.56)	0.06 (-0.91 - 1.04)	0.10 (-0.61 - 0.81)	-0.81 (-1.53 - -0.09)	**tongue protector**
League table for pain (consistency random-effects model adjusted for follow-up)					

Quality of life for all treatments, random effect. The lower part of the table shows the network estimates; the upper part of the table shows the direct estimates. The effectiveness estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Quality of life presents SMD with 95% Cl. Positive SMD values show that the row definition treatment is more effective than the intersection of the corresponding column definition treatment (more pain reduction). Negative SMD values mean that row definition treatment is less effective than column definition treatment (less pain reduction). Cells' colors represent the certainty of the evidence, from dark green (high), light green (moderate), dark yellow (low) to light yellow (very low).

Appendix Table 4. Summary of findings (SoF) table describing the effect estimates and the certainty of the evidence for the comparisons that did not enter the NMA.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	interventions	interventions or placebo	Relative (95% CI)	Absolute (95% CI)	
improvement of pain - laser compared to placebo											
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	11/13 (84.6%)	7/10 (70.0%)	**RR 1.21** (0.76 to 1.93)	**147 more per 1.000** (from 168 fewer to 651 more)	⊕◯◯◯ Very low
improvement of pain - phytotherapic compared to anxiolytic											
1	randomised trials	serious[c]	not serious	serious[a]	serious[d]	none	92/100 (92.0%)	69/100 (69.0%)	**RR 1.33** (1.16 to 1.54)	**228 more per 1.000** (from 110 more to 373 more)	⊕◯◯◯ Very low
pain - um-PEA comapred to placebo											
1	randomised trials	serious[e]	not serious	serious[a]	serious[d]	none	13	16	-	mean **3 lower** (3.63 lower to 2.37 lower)	⊕◯◯◯ Very low
improvement of pain - anxiolytic compared to phytotherapic											
1	randomised trials	serious[c]	not serious	serious[a]	serious[d]	none	69/100 (69.0%)	92/100 (92.0%)	**RR 0.75** (0.65 to 0.87)	**230 fewer per 1.000** (from 322 fewer to 120 fewer)	⊕◯◯◯ Very low
pain - cognitive therapy compared to no treatment											
1	randomised trials	not serious	not serious	not serious	serious[d]	none	15	15	-	MD **2.4 lower** (3.4 lower to 1.4 lower)	⊕⊕⊕◯ Moderate
improvement of pain - cognitive therapy compared to no treatment											
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	19/48 (39.6%)	6/48 (12.5%)	**RR 3.17** (1.39 to 7.23)	**271 more per 1.000** (from 49 more to 779 more)	⊕⊕◯◯ Low

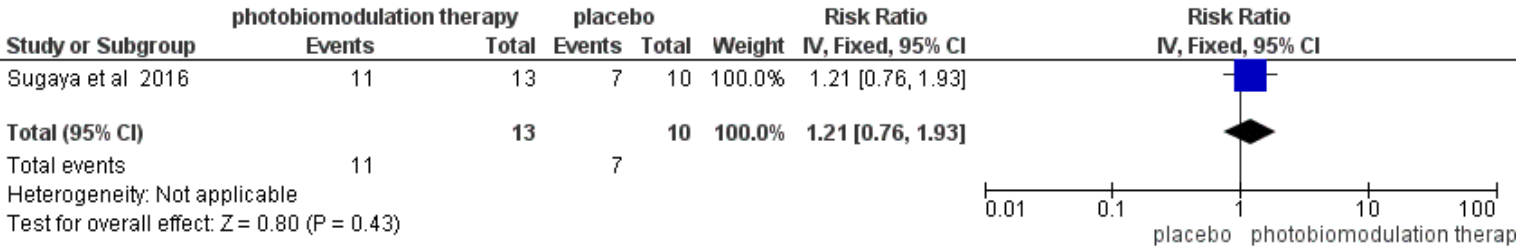
Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	interventions	interventions or placebo	Relative (95% CI)	Absolute (95% CI)	
pain - pregabaline compared to anxiolytic											
1	randomised trials	very serious[e,f]	not serious	serious[a]	serious[d]	none	25	25	-	MD **0.52 lower** (0.94 lower to 0.1 lower)	⊕◯◯◯ Very low
pain - pregabaline compared to ALA											
1	randomised trials	very serious[e,f]	not serious	serious[a]	serious[d]	none	25	25	-	**3 lower** (3.48 lower to 2.52 lower)	⊕◯◯◯ Very low
improvement of pain - GABA compareded to placebo											
1	randomised trials	serious[c]	not serious	serious[a]	serious[b]	none	10/20 (50.0%)	9/60 (15.0%)	**RR 3.33** (1.58 to 7.02)	**350 more per 1.000** (from 87 more to 903 more)	⊕◯◯◯ Very low
improvement of pain - GABA + ALA compared to placebo											
1	randomised trials	serious[c]	not serious	serious[a]	serious[d]	none	14/20 (70.0%)	9/60 (15.0%)	**RR 4.67** (2.39 to 9.09)	**551 more per 1.000** (from 209 more to 1.000 more)	⊕◯◯◯ Very low
pain - topical lubricant compared to placebo											
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	14	14	-	MD **1.7 lower** (3.41 lower to 0.01 higher)	⊕⊕◯◯ Low
improvement of pain - anti-inflammatory compared to placebo											
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	1/10 (10.0%)	2/10 (20.0%)	**RR 0.50** (0.05 to 4.67)	**100 fewer per 1.000** (from 190 fewer to 734 more)	⊕⊕◯◯ Low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

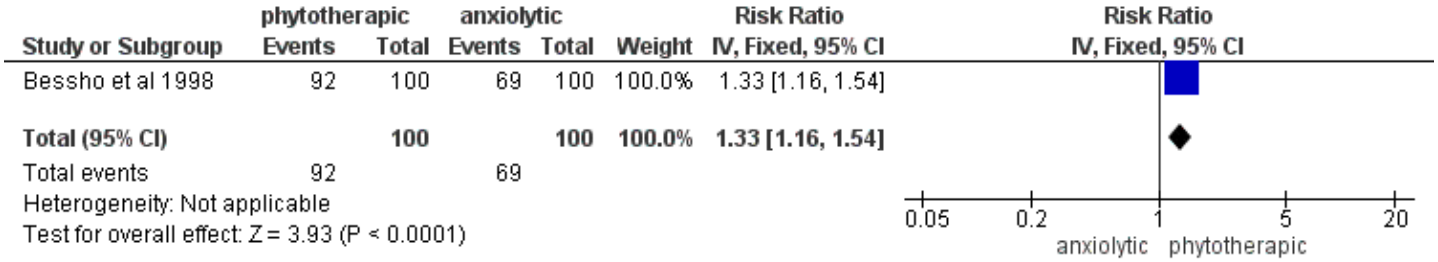
a. The treatment protocol tested cannot be applied in a generalized way
b. The sample does not fit the optimal information size (OIS) and the 95%CI crosses the threshold of minimally important difference.
c. Risk of bias due to failure in outcome measurement
d. The sample does not fit the optimal information size (OIS).
e. risk of bias due to missing outcome data
f. risk of bias due deviation from intended intervention

Forest plot 1



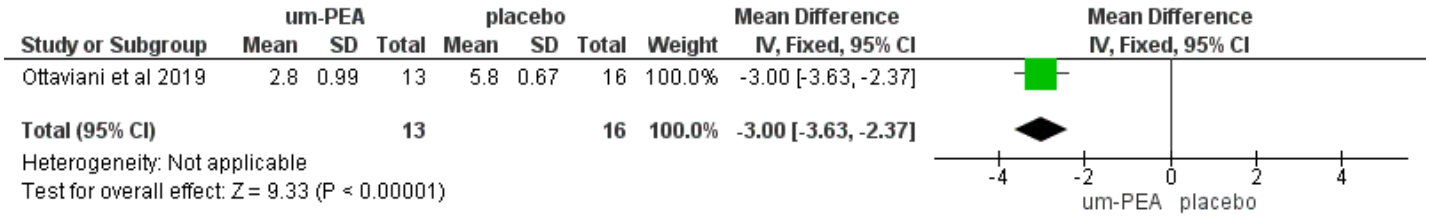
Meta-analysis for improvement of pain comparing photobiomodulation therapy (PBMT) with placebo.

Forest plot 2



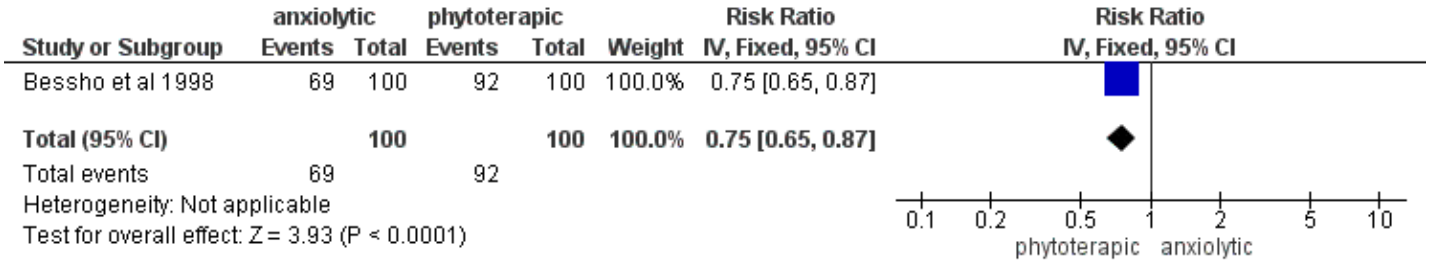
Meta-analysis for improvement of pain comparing phytotherapic with anxiolytic.

Forest plot 3



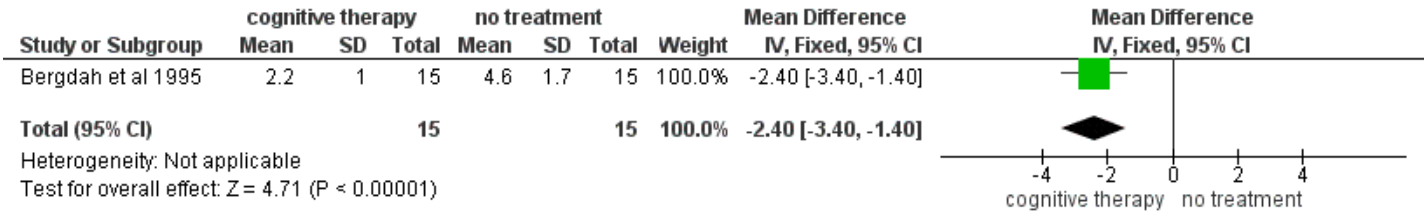
Meta-analysis for pain comparing um-PEA with placebo.

Forest plot 4



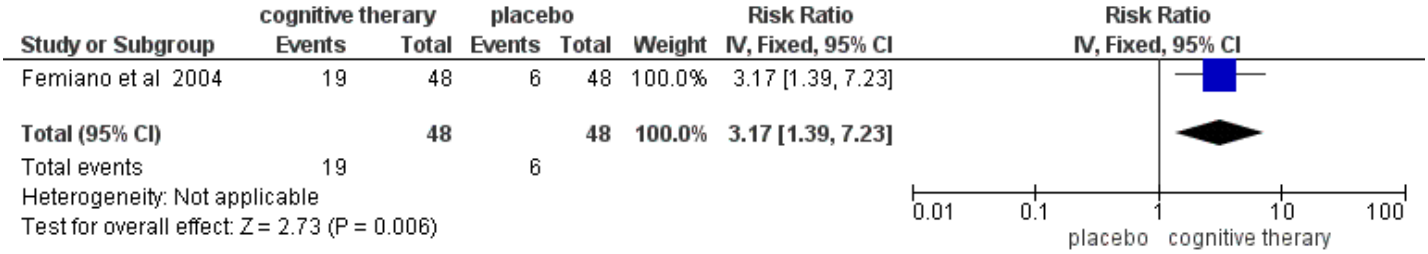
Meta-analysis for improvement of pain comparing anxiolytic with phytotherapic.

Forest plot 5



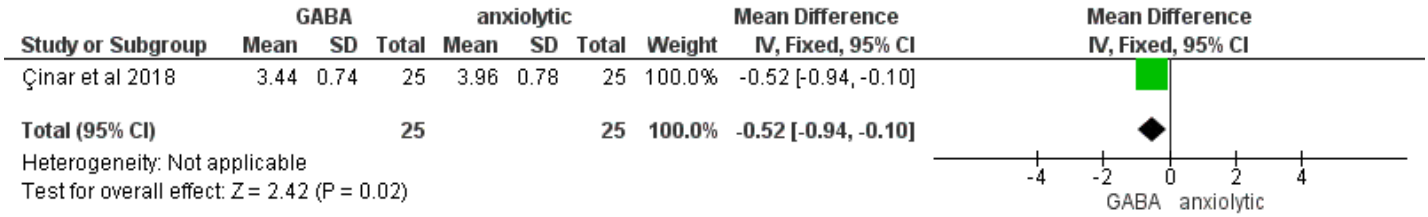
Meta-analysis for pain comparing cognitive therapy with no treatment.

Forest plot 6



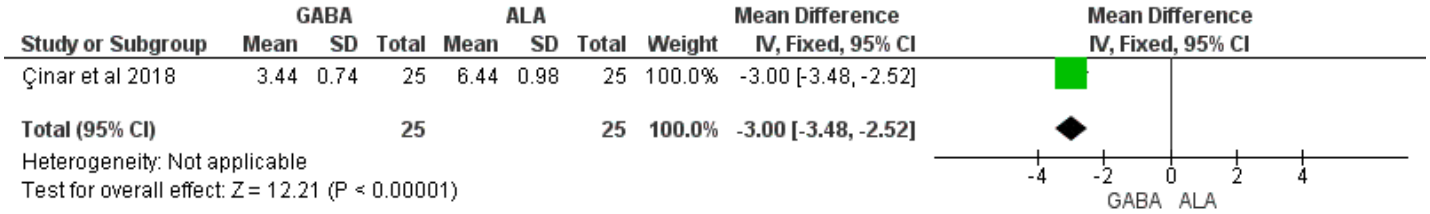
Meta-analysis for improvement of pain comparing cognitive therapy with placebo.

Forest plot 7



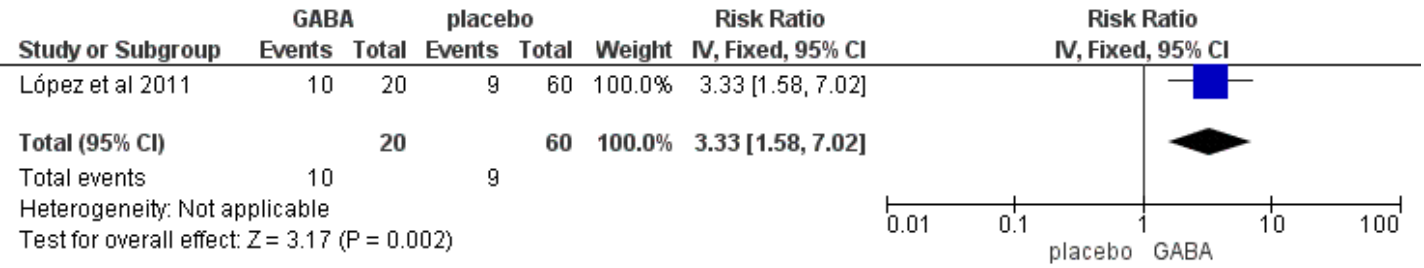
Meta-analysis for pain comparing gabapentin (GABA) with anxiolytic.

Forest plot 8



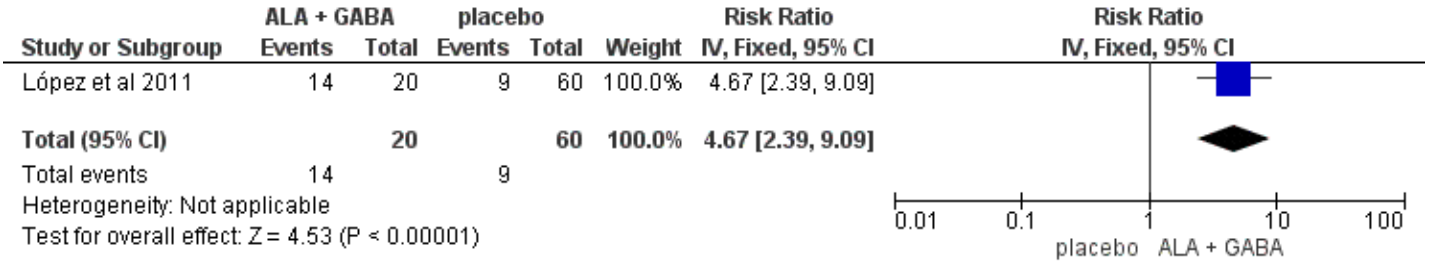
Meta-analysis for pain comparing gabapentin (GABA) with alpha-lipoic acid (ALA).

Forest plot 9



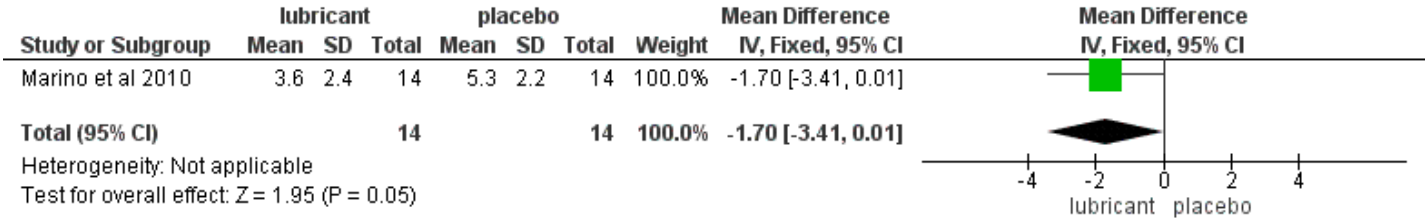
Meta-analysis for improvement of pain comparing gabapentin (GABA) with placebo.

Forest plot 10



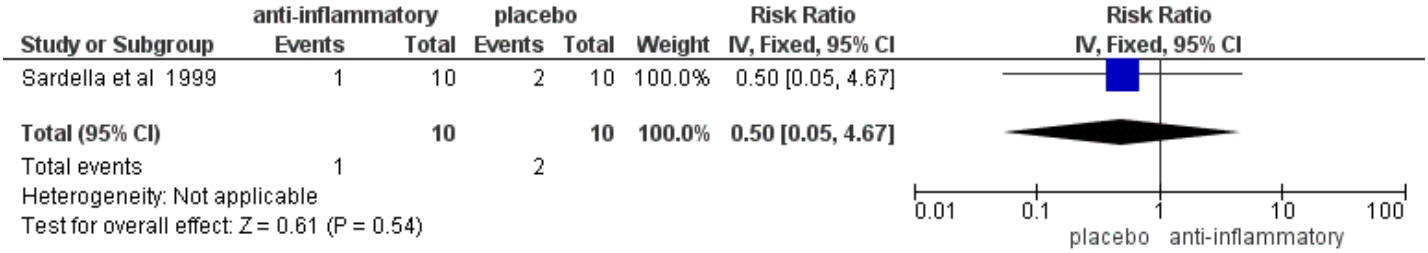
Meta-analysis for improvement of pain comparing gabapentin (GABA) + alpha-lipoic acid (ALA) with placebo.

Forest plot 11



Meta-analysis for pain comparing topical lubricant with placebo.

Forest plot 12



Meta-analysis for improvement of pain comparing anti-inflammatory (benzydamine hydrochloride) with placebo.

Box 1. Summary of narrative synthesis of 10 studies not included in the NMA.

Narrative synthesis	**Studies**
Comparable rate of improvement among photobiomodulation therapy compared to placebo; GABA compared to placebo; GABA + ALA compared to placebo; anti-inflammatory compared to placebo. All interventions were superior to placebo (n=3 studies)	(López-D'alessandro et al. 2011; Sardella et al. 1999; Sugaya et al. 2016)
Comparable rate of improvement - Superiority of phytotherapic against to anxiolytic (n=1 study)	(Bessho et al. 1998)
Comparable rate of improvement - Superiority of cognitive therapy against to no treatment (n=1 study)	(Femiano et al. 2004)
Pain improvement level - Superiority of um-PEA against to placebo. (n=1 study)	(Ottaviani et al. 2019)
Pain improvement level - Superiority of cognitive therapy against to no treatment (n=1 study)	(Bergdahl et al. 1995)
Pain improvement level - Superiority of pregabalin against to anxiolytic (n=1 study)	(Çınar et al. 2018)
Pain improvement level - Superiority of pregabalin against to ALA (n=1 study)	(Çınar et al. 2018)
Pain improvement level - Superiority of topical lubricant against to placebo (n=1 study)	(Marino et al. 2010)

Appendix Table 5. Secondary outcomes reported by studies.

Secondary outcome	Study	Intervention	MD (95%CI)*	Follow-up time
Salivary flow	(Heckmann et al., 2012)	anxiolytic (clonazepam)	-0.20 (-1.08; 0.68)	42 days
		placebo	-0.20 (-0.95; 0.55)	42 days
IL-6 levels	(Pezelj-Ribarić et al., 2013)	PBMT	0.26 (0.18; 0.34)	28 days
		placebo	0.03 (-0.03; 0.09)	28 days
TNF-α levels	(Pezelj-Ribarić et al., 2013)	PBMT	0.20 (0.11; 0.29)	28 days
		placebo	0.03 (-0.05; 0.12)	28 days

*MD: Mean difference meta-analyzed per treatment considering baseline to the last time point. PBMT: potobiomodulation therapy.

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5 CONSIDERAÇÕES FINAIS

A SAB ainda é uma condição pouco elucidada para clínicos e pesquisadores, o que torna o seu manejo, um procedimento complexo, com baixa assertividade. A falta de um conhecimento mais claro sobre a etiopatogenia desta síndrome, potencializada pela dificuldade do diagnóstico, torna o seu tratamento um ponto central de controvérsias.

Esta revisão sistemática levantou diversos ensaios clínicos controlados randomizados, que avaliaram a mais variada gama de agentes farmacológicos e terapêuticos. Porém, devido a um risco de viés aumentado na maioria dos estudos analisados, alta heterogeneidade entre os estudos e pequeno número de participantes nas amostras, a certeza da evidência foi baixa ou muito baixas para a maioria das terapias. Assim, a eficácia da maioria delas ainda é incerta.

O clonazepam é um benzodiazepínico com efeito inibitório no sistema nervoso central, comumente usado como agente ansiolítico. Ele, provavelmente, reduz a sensação de queimação da SAB. Tanto a ingestão oral quanto a aplicação tópica de clonazepam mostraram resultado favorável no alívio da dor na SAB. Alguns estudos relataram efeitos adversos, mas, estes, não afetaram o curso dos tratamentos. No entanto, a aplicabilidade relacionada à eficácia, efeitos adversos e qualidade de vida foram limitados a 120 dias.

Neste cenário, sugerimos que novos ensaios clínicos sejam conduzidos, utilizando técnicas terapêuticas comparadas ao placebo. Entretanto, deve-se levar em consideração, os efeitos adversos provocados por estas drogas. Faz-se necessário também, um rigor metodológico na condução destes trabalhos, a fim de se dirimir as dúvidas persistentes.

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ANEXO A - Protocolo PROSPERO

PROSPERO PROTOCOL

Efficacy of different treatments for burning mouth syndrome: systematic review

Rachel Alvarenga-Brant, Carolina Castro Martins, Gustavo Mattos-Pereira, Loukia Spineli, Ricardo Santiago Gomez, Fernando Oliveira Costa.

Citation

Review question

To perform a systematic review and search for the scientific evidence of the efficacy of all types of treatments for the relief of symptoms of burning mouth syndrome (BMS): e.g. herbal medicines, chamomile, catuama, artificial saliva, laser, antidepressant and others.

Searches

A search will be performed in the following databases: MedLine through Ovid, Embase through Ovid, Cochrane Database of Systematic Reviews and Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, Clinical Trials, International Clinical Trials Regitry Plataform (ICTRS), Dissertation database (Proquest Dissertation & theses database).
A manual search will be conducted in the list of references of included studies. There will be no restrictions regarding the date of publication and language.

The search strategies will be created using Mesh terms and free terms for each database.

Types of study to be included

Randomized controlled trials (RCTs).

Exclusion criteria: quasi-randomized studies, non-randomized studies, observational case-control studies and trials withouth a comparison group.

Condition domain being studied

Burning mouth syndrome (BMS)

Participants/ population

We will include: adults above 18 years-old, from both genders, diagnosed with burning mouth syndrome by a dentist or oral health profession using validated criteria.

We will exclude: patients below 18 years-old; pregnant or lactating women, patients with the following pathologies: lesions of the oral mucous membranes, systemic diseases such as diabetes, anemia, vitamin B1, B2, B6, B12, Fe, Zinc and folic acid deficiency; gastroesophageal reflux, patients undergoing previous head and neck radiotherapy, Sjogren's disease, syndromes, allergies, candidiasis and hyposalivation.

Intervention(s), exposure: Topical application of herbal medicines (such as chamomile, catuama, aloe vera, capsaicin, hypericum perforatum and others), artificial saliva, topical application of laser, oral medications (such as antidepressant, melatonine, alpha-lipoic acid, gabapentin), acupuncture, when reported.

Comparator(s)/control

Placebo or no treatment

Main outcome(s)

Pain and burning sensation measured before and after the treatment

Measures of effect

Additional outcome(s):

Side effects, quality of life, salivary flow, TNF-α and IL-6 levels, when reported by trials.

Measures of effect:

For continuous outcomes, we will consider the mean difference of change to baseline. If the trials use different approaches to measure the outcome, we will consider the ratio of ratio of the last point to baseline means or standardized mean difference using an internal reference standard deviation (SMDi) as recommended by Daly et al. 2021. We will investigate whether the treatment effects are proportional following the recommendations of Daly et al. (section 5.1, there). If the assumption of proportionality does not hold, we will apply SMDi. For binary outcomes, we will apply the odds ratio (in the logarithmic scale) for its preferred statistical properties.

Data extraction (selection and coding):

Two independent reviewers will independently extract data following an abstraction excel spreadsheet. Data will be extracted regarding local that the study took place, language, type of treatment, follow-up, clinical score used for pain or burning sensation; dropouts; final estimates, funding, conflict of interest. For continuous variables, we will collect means, standard deviations, standard errors, 95%CI. For categorical events, we will collect the frequency of patients reporting pain, OR, RR, 95%CI.

Risk of bias (quality) assessment

The risk of bias of will be evaluated through the Revised tool to assess Risk of Bias in Randomized Trials (RoB 2.0) (Sterne et al. 2019). It is expected to find some unblinded studies

Strategy for data synthesis

We expect to find several types of treatments, and the common comparator or placebo group might not be the same among trials. The treatment arms can include antidepressants (oral pills), natural agents (topical mouth rinse), laser (topical application), and others. It can be difficult to defend the transitivity due to the different nature of the interventions. E.g. the placebo group for laser can mimick laser application on oral tissue, whereas the placebo from oral antidepressants pills can be a placebo white-colored pill. By this way, the network meta-analysis (NMA) can be unfeasible if the comparator is fundamentally different in the compared sets of trials and the administration routes, therefore not allowing valid indirect comparisons (Salanti, 2012). In this way, we plan to consider several subgroups of networks according to the administration route of the treatment: topical application as a mouth rinse (e.g. natural agents), topical application of laser, oral pills (antidepressants, anticonvulsants and others). If the networks are not connected or consist of comparisons informed by a single trial, we will abstain from NMA. Instead, in the first case, we will perform several random-effects pairwise meta-analyses, provided that the comparisons include at least two trials. In the latter case, we will estimate the within-trial results (average treatment effect and standard error), and we will create a panel of forest plots for each observed comparison.

If NMA is possible, we will prefer a one-stage Bayesian random-effects NMA with a consistency equation and proper accommodation of the multi-arm trials (Dias et al. 2013). In the presence of missing outcome data, we will model observed and missing outcome data simultaneously via the pattern-mixture model (Spineli 2019; Spineli et al. 2021). If there are closed loops of interventions not informed by multi-arms exclusively, we will investigate the consistency assumption locally via the node-splitting approach (Dias et al. 2010; van Valkenhoef et al. 2016) and globally via the unrelated mean effects model (Dias et al. 2013). In line with NMA, we also consider one-stage Bayesian random-effects model for the pairwise meta-analyses with incorporation of missing outcome data (if present) via the pattern-mixture model.

The certainty of evidence will be assessed through Grading of Recommendations, Assessment, Development and Evaluation approach (GRADE) (Guyatt et al. 2008).

Analysis of subgroups or subsets:

If there are enough trials to allow for a moderator analysis, we will perform random-effects meta-regression bydose and age, separately, assuming exchangeable regression coefficients (Cooper et al. 2009). We will also investigate the presence of small-study effects following the methods proposed by Chaimani et al. 2012. In case of evidence of small-study effect, we will investigate the possibility of publication bias via a design-by-treatment selection model (Mavridis et al. 2014)

We plan to run a sensitivity analysis excluding studies with a high risk of bias and studies funded by industry. We will use the robustness index of summary effect estimates to conclude objectively on the robustness of the primary analysis results after excluding the trials above (Spineli et al. 2021).

Contact details for further information:

Rachel Alvarenga-Brant
kekelbrant@yahoo.com

Organizational affiliation of the review:

Universidade Federal de Minas Gerais

Review team members and their organizational affiliations.

Mrs Rachel Alvarenga-Brant – Universidade Federal de Minas Gerais - MSc student
Dr Carolina Castro Martins - Universidade Federal de Minas Gerais - Professor
Mr Gustavo Mattos-Pereira - Universidade Federal de Minas Gerais – PhD candidate
Dr Loukia Spineli - Midwifery Research and Education Unit, Hannover Medical School, Hannover – Postdoctoral researcher
Dr Ricardo Santiago Gomez - Universidade Federal de Minas Gerais - Professor
Dr Fernando Oliveira Costa - Universidade Federal de Minas Gerais - Professor

Type and method of review:

Epidemiologic, Intervention, Systematic review

Anticipated or actual start date:

01/05/2021

Anticipated completion date:

31/07/2022

Funding sources/sponsors:

CAPES post-doctoral fellowship (Coordination for the Improvement of Higher Education Personnel, BRAZIL)

Conflicts of interest

None

Language

Country:

Brazil, Germany

Stage of review:

Not started

Details of final report/publication(s) or preprints if available:

Other information

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ANEXO B - Comprovante de submissão

ENC: Journal of Dental Research JDR-22-0580

De: Carolina Martins (carolcm10@hotmail.com)

Para: kekelbrant@yahoo.com

Data: sábado, 18 de junho de 2022 12:28 BRT

De: Journal of Dental Research <onbehalfof@manuscriptcentral.com>
Enviado: quinta-feira, 16 de junho de 2022 10:48
Para: kekelbrant@yahoo.com <kekelbrant@yahoo.com>; focperio@uol.com.br <focperio@uol.com.br>; ghmattos75@gmail.com <ghmattos75@gmail.com>; rafaelpaschoalesteves@yahoo.com.br <rafaelpaschoalesteves@yahoo.com.br>; fevieirabelem@yahoo.com.br <fevieirabelem@yahoo.com.br>; 15887217913@163.com <15887217913@163.com>; gelong2009@163.com <gelong2009@163.com>; rsgomez@ufmg.br <rsgomez@ufmg.br>; carolcm10@hotmail.com <carolcm10@hotmail.com>
Assunto: Journal of Dental Research JDR-22-0580

16-Jun-2022

Dear Dr. MARTINS:

Your manuscript entitled "Treatments for burning mouth syndrome: a network meta-analysis" has been successfully submitted online and is presently being given full consideration for publication in Journal of Dental Research.

Your manuscript ID is JDR-22-0580.

You have listed the following individuals as authors of this manuscript:
Alvarenga-Brant, Rachel; Costa, Fernando; Mattos Pereira, Gustavo Henrique; Esteves Lima, Rafael; Belém, Fernanda; Lai, Honghao; Ge, Long; Gomez, Ricardo; MARTINS, CAROLINA

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://mc.manuscriptcentral.com/jdr and edit your user information as appropriate.

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Thank you for submitting your manuscript to Journal of Dental Research.

Sincerely,
JDR Editorial Office
Journal of Dental Research
jdr@iadr.org

ANEXO C - Normas para publicação

The *Journal of Dental Research (JDR)* adheres to the CSE (8th Edition) editorial style. All submitted manuscripts should be formatted in this style

The *Journal of Dental Research* (*JDR*) is a peer-reviewed scientific journal dedicated to the dissemination of new knowledge and information on all science relevant to dentistry and to the oral cavity and associated structures in health and disease. The *Journal of Dental Research*'s primary readership consists of oral, dental and craniofacial researchers, clinical scientists, hard-tissue scientists, dentists, dental educators, and oral and dental policy-makers. The *Journal* is published monthly, allowing for frequent dissemination of its leading content. The *Journal of Dental Research* also offers OnlineFirst, by which forthcoming articles are published online before they are scheduled to appear in print.

Authors of all types of articles should be aware of the following guidelines when submitting to JDR.

ONLINE SUBMISSION

Submissions to the *Journal of Dental Research* are only accepted for consideration via the SAGETrack online manuscript submission site at http://mc.manuscriptcentral.com/jdr. Authors who do not have an active account within the system are required to create a new account by clicking, "Create Account," on the log-in page. The system will prompt the authors through a step by step process to create their account. Once created authors can submit their manuscripts by entering their "Author Center" and clicking the button by "Click Here to Submit a New Manuscript."

If any difficulty is encountered at any time during the account creation or submission process, authors are encouraged to contact the *Journal of Dental Research* at jdr@iadr.org.

MANUSCRIPT REQUIREMENTS BY TYPE

The *Journal of Dental Research* accepts the following types of manuscripts for consideration:

Original Research Reports: These manuscripts are based on clinical, biological, and biomaterials and bioengineering subject matter. Manuscripts submitted as research reports have a limit of 3,200 words (including introduction, materials, methods results, discussion and; excluding abstracts, acknowledgments, figure legends and references); a total of 5 figures or tables; 40 references; and must contain a 300 word abstract.

Letters to the Editor*: Letters must include evidence to support a position about the scientific or editorial content of the *JDR*. Manuscripts submitted as a letter to editor have a limit of 250 words. No figures or tables are permitted. Letters on published articles must be submitted within 3 months of the article's print publication date.

Guest Editorials*: A clear and substantiated position on issues of interest to the readership community can be considered for this manuscript type. Guest Editorials are limited to 1,000 words. No figures or tables are permitted.

Discovery!: Essays that explore seminal events and creative advances in the development of dental research are considered for the "Discovery!" section of the

journal. Manuscripts submitted for "Discovery!" have a limit of 2,500 words and a total of 2 figures or tables. Manuscripts are to be submitted by invitation only.

Critical Reviews in Oral Biology & Medicine: These manuscripts should summarize information that is well known and emphasize recent developments over the last three years with a prominent focus on critical issues and concepts that add a sense of excitement to the topic being discussed. Manuscripts are to be submitted by invitation only. Authors interested in submitting to this section must contact the Editor of *Critical Reviews in Oral Biology & Medicine*, Dr. Dana Graves, at dgraves@iadr.org for submission approval and instructions. Manuscripts submitted as Critical Reviews have a limit of 4,000 words; a total of 6 figures or tables; 60 references; and must contain a 300 word abstract.

Additional Instructions for Critical Reviews:

-It is important to include several illustrations or diagrams to enhance clarity. Manuscripts that lack figures or diagrams typically receive a low priority score.

-Summarize important concepts in tables or flow charts or show critical data in the form of figures. NOTE: authors will need to obtain permission to reproduce a previously published figure or table.

-Due to the broad readership, abbreviations commonly recognized in one field may not be readily apparent to those in a different field. Keep abbreviation use to a minimum.

-The cover page, abstract, text, summary, figure legends, and tables should be combined into a single Word document. Figures should be submitted as a separate document.

-To view examples of recent Critical Reviews in the Journal, please click the following links:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3318079/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3327727/

***Brief responses to Letters to the Editor or Guest Editorials will be solicited for concurrent publication.**

Clinical Reviews (formerly Concise Reviews): These manuscripts are generally systematic reviews of topics of high clinical relevance to oral, dental and craniofacial research. Meta-analyses should be considered only when sufficient numbers of studies are available. Manuscripts that include investigations of limited study quality of under-studied areas are typically not acceptable as topics for a clinical review. Although some systematic reviews may be well done, those that receive highest scientific priority will only be considered given the very limited space allowed for these reviews in the journal.

Manuscripts submitted as Clinical Reviews have a strict limit of 4,000 words (including introduction, materials, methods results, discussion and; excluding abstracts , acknowledgments, figure legends and references); a total of 6 figures or tables; up to a maximum of 60 references; and must contain a 300 word abstract. Manuscripts above the 4,000 word/6 figure or table limit may use supplemental appendices for other supporting information that would be available online only.

Additional Instructions for Clinical Reviews:

-It is important to include illustrations or diagrams to enhance clarity. Manuscripts that lack figures or diagrams typically receive a low priority score.

-Summarize important concepts in tables or flow charts or show critical data in the form of figures. NOTE: authors will need to obtain permission to reproduce a previously published figure or table.

-Due to the broad readership, abbreviations commonly recognized in one field may not be readily apparent to those in a different field. Keep abbreviation use to a minimum.

-The cover page, abstract, text, summary, figure legends, and table(s) should be combined into a single Word document. Figures should be submitted as a separate document.

-To view examples of recent Clinical Reviews in the Journal, please click the following links: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613886/ or https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5004242/

All submissions must include a title page and be accompanied by a cover letter and list of suggested reviewers. Cover letters should certify the research is original, not under publication consideration elsewhere, and free of conflict of interest. Title pages should include: abstract word count, total word count (Abstract to Acknowledgments), total number of tables/figures, number of references, and a minimum of 6 keywords. Keywords cannot be words that have been included in the manuscript title. Key words should be selected from Medical Subject Headings (MeSH) to be used for indexing of articles. See: http://www.nlm.nih.gov/mesh/MBrowser.html for information on the selection of key words.

Please submit the names and email addresses of four preferred reviewers when prompted by the SAGETrack system. Preferred reviewers cannot be colleagues at the contributors' institution or present or former collaborators.

TITLES

Titles can consist of a maximum of 75 characters (including spaces). Titles do not normally include numbers, acronyms, abbreviations or punctuation. The title should include sufficient detail for indexing purposes but be general enough for readers outside the field to appreciate what the paper is about.

ACKNOWLEDGMENTS

Authors are required to report all sources of support for their project or study, including but not limited to: grant funds, commercial sources, funds from a contributors' institution. Do not refer to a study being "partially funded by the cited sources." Consultancies and funds paid directly to investigators must also be listed. Authors are required to specify during the submission process if their paper received funding from NIH, NIDCR, or any other NIH Institute or Center and provide the grant number. To comply with the NIH Public Access Mandate, for qualifying NIH- funded papers, the *Journal of Dental Research* will deposit the final, copyedited paper to PubMed Central on behalf of the authors.

Any perceived or actual conflicts of interest need to be identified in the acknowledgments section. The *JDR* abides by the International Committee of Medical Journal Editors guidelines for the Ethical Considerations in the Conduct and Report of Research (http://www.icmje.org). Authors are requested to include this information in the acknowledgments section and the corresponding author must confirm that all co-authors have reported any potential conflicts.

Authors are required to provide a written statement of author contributions as part of your Acknowledgements. Include as many authors as you have, note their completed roles, and conclude with the following statement. "All authors gave their final approval and agree to be accountable for all aspects of the work."

For example:

Author contributions

Author 1: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript

Author 2: Contributed to conception, design, data acquisition and interpretation, performed all statistical analyses, drafted and critically revised the manuscript

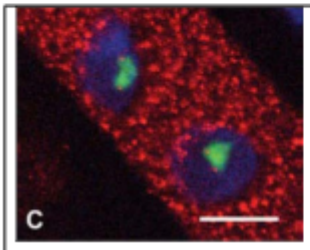
Author 3: Contributed to conception, design, and critically revised the manuscript

FIGURE AND TABLE REQUIREMENTS

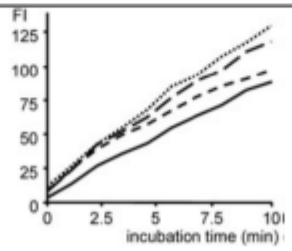
These guidelines are intended to aid authors in providing figures that will reproduce well in both print and online media. Submitting digital image files that conform to these guidelines will prevent delays in the review and publication processes, and maximize the published quality of your figures.

Figure Types

JDR figures can fall into one of three categories: **Continuous-tone images**, **Line-art images**, and **Combination images.** Each image type has specific requirements in terms of the resolution needed for publication and the file types best suited for the figure. See the following panels for examples and requirements.



Continuous-tone Image
Minimum resolution: 300dpi.
Preferred File Formats: TIFF, Bitmap.



Line-art Image
Minimum resolution: 800dpi.
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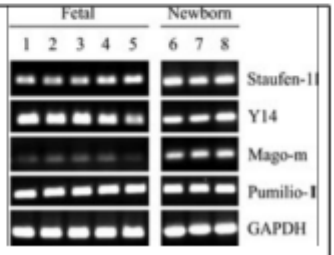

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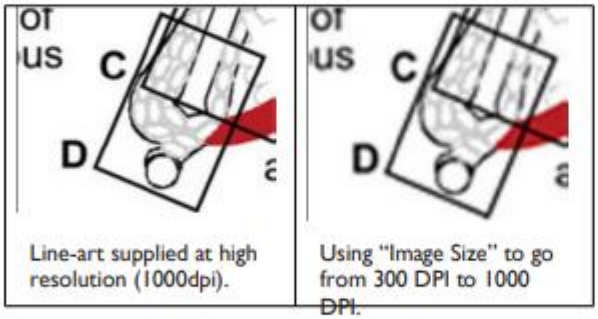
Minimum resolution: 800dpi.
Preferred File Formats: PDF, EPS,
PowerPoint, Illustrator, InDesign

Resolution

In order for a figure to be used in publication, its Digital Image File must have the required resolution when it is created. The resolution cannot be raised *after* the original image is made. Attempting to do so (for example, with Adobe Photoshop's© "*Image Size*" command) results in the addition of artificial pixels that distort the image and lower its sharpness. The figures on the right show an example of this reduced sharpness.



Line-art supplied at high resolution (1000dpi).

Using "Image Size" to go from 300 DPI to 1000 DPI.

Image Integrity Guidelines

The International Committee of Medical Journal Editors (ICMJE) recommendations note that scientific misconduct includes deceptive manipulation of images. Figures submitted to the *Journal of Dental Research* should be minimally processed and should reflect the integrity of the original data in the image(s). Adjustments to images in brightness, contrast, or color balance should be applied equally to the entire image, provided they do not distort any data in the figure, including the background. Selective adjustments and touch-up tools used on portions of a figure are not appropriate. Images should not be layered or combined into a single image unless it is stated that the figure is a product of time-averaged data. In the case of gel images, the grouping of lanes from different gels, fields or exposures must be made explicit by the arrangement of the figure (e.g. by the use of the dividing lines). All adjustments to image data, including the grouping of lanes from gels, should be clearly disclosed in the figure legend. Images may be additionally screened to confirm faithfulness to the original data. If original data cannot be provided by an author when requested, acceptance of the manuscript may be revoked. Authors are expected to supply raw image data upon request. Authors should also list tools and software used to collect image data and should document settings and manipulations in the Methods section.

These guidelines were derived from those provided by the *Journal of Cell Biology* and *Nature*:

http://jcb.rupress.org/editorial-policies#data-integrity

https://www.nature.com/authors/policies/image.html

Experimental controls

Appropriate controls should be provided for all experimental methods. For example, negative controls are needed for immunofluorescence (IF) and immunohistochemistry (IHC), i.e. control primary antibody or antibody plus excess antigen, which can be added as supplemental data. In addition, arrows should identify representative immunopositive cells that are clearly distinguished from background staining in IF and IHC images.

Fonts

Limit fonts used in any figure to Times, Times New Roman, Arial, Frutiger, and Sabon.
Other fonts cannot be guaranteed to reproduce properly.

Files containing figures and tables should be clearly labeled to indicate their placement in the text or appendix. Tables should be viewable in a portrait view. Tables that are created in a landscape view are more suitable for an appendix.

If the online version is in color and the printed version in black and white, please submit separate files for each version. Figures should be identical except in color or grayscale. The cost of color figures in the print version will be borne by the authors. Rates for color reproduction are $300 per initial page of color and $150 for each additional page of color. However, there are no charges for figures and diagrams printed in black and white. Color figures many be included in the online version of *JDR* with no extra charges.

REFERENCES

The *Journal of Dental Research (JDR)* adheres to the CSE (8th Edition) editorial style. All submitted manuscripts should be formatted in this style: http://www.scientificstyleandformat.org/Tools/SSF-Citation-Quick-Guide.html.

SUPPLEMENTAL FILES

Additional supporting data may be referenced as a supplemental appendix for publication online only. All supplemental appendix files must be submitted with the manuscript for review. Supplementary files will be subjected to peer-review alongside the article.

Supplementary files will be uploaded as supplied. They will not be checked for accuracy, copyedited, typeset or proofread. The responsibility for scientific accuracy and file functionality remains with the authors. A disclaimer will be displayed to this effect with any supplementary material published. Supplemental files may include additional figures or tables that exceed the Journal's limit. Material intended for the supplemental appendix must have "supplemental" or "appendix" in the file name upon upload. When formatting your supplemental files, please follow these instructions:

- Authors should provide a single Word file with all Appendix content. Figures and tables should be included in the main Appendix file so they can appear immediately alongside their captions. High resolution figures may also be supplied separately if authors wish, but they also must be copied into the Word file so everything can be kept together.
- Be sure to run spell check and proofread the text.
- Remove all highlighting/other colors. Use one font throughout.
- The Appendix should include the title of the article and all authors. Page numbers are recommended.
- Figures and Tables should be labeled Appendix Figure/Table 1, Appendix Figure/Table 2, etc. Avoid labeling as S1, S2, and so forth.
- All table footnotes and figure legends should be included.
- Preferably, authors shouldn't label separate parts as "Appendix 1", "Appendix 2", etc.; just use section heads as in a regular article.

Language Editing: Manuscripts submitted for publication consideration should be written in English. Prior to submission, if a manuscript would benefit from professional editing, authors may consider using a language-editing service. Suggestions for this type of service can be found at www.iadr.org/EditingServices. The *Journal of Dental Research* does not take responsibility for, or endorse these services, and their use has no bearing on acceptance of a manuscript for publication.

GENERAL INFORMATION FOR AUTHORS SUBMITTING A MANUSCRIPT

PRIOR PUBLICATION

Manuscripts submitted to the *Journal of Dental Research* are accepted for consideration giving the understanding that it contains original material that has not been submitted for publication or has been previously published elsewhere. Any form of publication other than an abstract only constitutes prior publication.

Manuscripts posted or submitted to a non-commercial preprint server are not considered previously published. Submitting authors will be required to disclose if the manuscript has been posted or submitted to a non-commercial preprint server.

ICMJE COMPLIANCE STATEMENT

Manuscript submission guidelines for the *Journal of Dental Research* follow the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" set forth by the International Committee of Medical Journal Editors (ICMJE). For additional information please visit the ICMJE web site at http://www.icmje.org/.

CONSORT 2010 CHECKLIST COMPLETION RANDOMIZED CLINICAL TRIALS POLICY

Manuscripts reporting a randomized clinical trial are required to follow the CONSORT guidelines. The Journal requires authors of studies involving laboratory animals submit with their manuscript the full version of the Animal Research: Reporting In Vivo Experiments (ARRIVE) 2.0 checklist. Authors of human observations studies in epidemiology are required to review and submit a STROBE statement. When uploaded to the SAGETrack system, any checklists completed by authors should be given a supplementary file designation. Authors who have completed the ARRIVE or STROBE checklist should include as the last sentence in the Methods section a sentence stating compliance with the appropriate guidelines/checklist.

Additional guidance on compliance with various research guidelines can be found on the Guideline Information - Enhancing the Quality and Transparency of Health Research: www.equator-network.org.

The CONSORT checklist can be downloaded from:
http://www.equator-network.org/reporting-guidelines/consort/

The ARRIVE guidelines can be found here:
https://arriveguidelines.org/resources/author-checklists
The STROBE checklists can be found here:
www.strobe-statement.org/index.php?id=strobe-home

The *Journal of Dental Research* requires authors to register their clinical trials in a public trials registry. Authors of manuscripts describing such studies are asked to submit the name of the registry and the study registration number prior to publication. Authors are asked to include their clinical trial registration number at the end of their abstracts. In accordance with the aforementioned "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," clinical trials will only be considered for publication if they are registered.

INSTITUTIONAL REVIEW BOARD AND WRITTEN INFORMED CONSENT

For protocols involving the use of human subjects, authors should indicate in their Methods section that subjects' rights have been protected by an appropriate Institutional Review Board and written informed consent was granted from all subjects. When laboratory animals are used, indicate the level of institutional review and assurance that the protocol ensured humane practices.

PUBLIC GENE DATA

Prior to submission, the *Journal of Dental Research* asks that novel gene sequences be deposited in a public database and the accession number provided to the Journal. Authors may want to use the following Journal approved databases:

GenBank: www.ncbi.nlm.nih.gov/Genbank/submit.html

EMBL: www.ebi.ac.uk/embl/Submission/index.html

DDBJ: https://www.ddbj.nig.ac.jp/index-e.html

Manuscript submissions including microarray data should include the information recommended by the MIAME guidelines in their submission, and/or identify the submission details for the experiments details to one of the publicly available databases such as Array Express or GEO. Information on MIAME, Array Express and GEO can be found by clicking on the corresponding links below:

MIAME: http://fged.org/projects/miame/

ArrayExpress: http://www.ebi.ac.uk/arrayexpress

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