International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
https://theaspd.com/index.php

Effectiveness of Alpha Lipoic Acid and Pregabalin, for the Treatment of Burning Mouth Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

Jamal Qader Ahmed (MSc, FKHCMS)[1]
[1]Lecturer, College of Dentistry, Hawler Medical University, Erbil, Iraq
Corresponding Author:
Jamal Qader Ahmed
College of Dentistry, Hawler Medical University, Erbil, Iraq
Email: Jamal.qadir@hmu.edu.krd

Abstract

Background: *Burning mouth syndrome (BMS) is a chronic neuropathic pain disorder with no clear etiology. Alpha-lipoic acid (ALA) and pregabalin are individually used to manage neuropathic pain, but their combined effect in BMS remains underexplored.*

Objective: *To evaluate and compare the therapeutic efficacy and safety of ALA, pregabalin, and their combination versus placebo in BMS patients.*

Methods *In a double-blind, randomized controlled study, 40 patients with Burning Mouth Syndrome (BMS) were assigned to four groups, each receiving medicine for a duration of two months as follows: pregabalin (300 mg/day), ALA (600 mg/day), combination therapy (ALA + pregabalin), and placebo. Burning intensity was measured using a custom 0–4 geographic burning scale and VAS score at baseline, 1 month, and 2 months. Safety was assessed via adverse effects of medications reporting and laboratory tests.*

Results: *After 2 months, favorable outcomes were observed in 10% (placebo), 60% (ALA), 80% (pregabalin), and 90% (combination therapy) of patients. Combination therapy yielded the highest odds of symptom improvement (OR = 81; $p < 0.001$). Side effects were mild and comparable across all groups.*

Conclusion: *Both ALA and pregabalin significantly reduced BMS symptoms, with combination therapy showing superior efficacy. These findings suggest synergistic neuroprotective effects and support further large-scale, long-term studies.*

Keywords: *Burning mouth syndrome, Alpha lipoic acid, Pregabalin,*

INTRODUCTION

Burning Mouth Syndrome (BMS) is a chronic, idiopathic illness marked by a continuous burning sensation in the oral mucosa, devoid of any observable clinical indicators or discernible medical or dental etiology (1-3). The burning sensation predominantly impacts the tongue—especially its tip and lateral edges—but may also extend to the lips, palate, and other regions of the oral cavity. Additional symptoms encompass altered taste sensations (dysgeusia), xerostomia (dry mouth), and oral discomfort (4, 5).

BMS predominantly affects peri- and postmenopausal women, generally over the age of 50, with a markedly higher frequency in females compared to males (6). The precise etiology is unclear; however, the condition is generally regarded as multifactorial, including peripheral or central neuropathic mechanisms, hormonal variations, nutritional deficiencies (e.g., iron, folic acid, vitamin B12), psychological factors such as anxiety and depression, and local irritants (7, 8).

Alpha-lipoic acid (ALA) has attracted interest for its antioxidant and neuroprotective properties among the suggested therapies. ALA is a naturally occurring dithiol molecule that functions as a coenzyme in mitochondrial oxidative metabolism and contributes to neural regeneration and the detoxification of reactive oxygen species. Certain clinical investigations have indicated its potential efficacy in alleviating neuropathic pain symptoms, especially those associated with BMS (9, 10).However, the evidence seems inconsistent, since multiple research and reviews indicate no statistically significant difference when compared to placebo (10-12).

Pregabalin, a structural equivalent of gamma-aminobutyric acid (GABA), is a medication that has demonstrated efficacy in neuropathic pain syndromes. It regulates calcium channel activity in the central nervous system, thus diminishing the release of certain excitatory neurotransmitters implicated in pain transmission. Its application in BMS has been corroborated by limited investigations, however it remains inadequately established (13, 14).

Considering the possible neuropathic origin of BMS and the distinct advantages of both ALA and pregabalin, it is reasonable to suggest that a combination of these drugs may offer improved symptom alleviation through synergistic processes (14, 15).
This study aimed to assess and compare the treatment effectiveness of alpha-lipoic acid, pregabalin, and their combination in patients with burning mouth syndrome.

MATERIALS and METHODS

Study Design and Setting

A double-blind, randomized clinical trial was conducted involving 40 patients diagnosed with Burning Mouth Syndrome (BMS). Participants were recruited from the Oral Medicine Clinic at Khanzad Teaching Dental Center and Hawler Psychiatric Hospital and Consultation in Erbil City. The diagnosis of BMS was established following the exclusion of all identifiable organic etiologies.

Inclusion and Exclusion Criteria

The criteria for inclusion were as follows: (1) individuals aged 18 years or older; (2) those who have experienced burning pain in the oral mucosa for over 2 hours daily for a duration exceeding 3 months as their primary complaint; (3) individuals exhibiting no discernible abnormalities on the oral mucosal surface during clinical evaluation; and (4) those with no identified local or systemic etiologies for the burning pain in the oral mucosa, including oral mucositis, oral candidiasis, geographic tongue, Sjögren's syndrome, diabetes mellitus, or anemia.
Patients on polypharmacy, defined as those using more than three systemic medications daily, were excluded from the study. This exclusion applied specifically to individuals taking psychotropic and antihypertensive drugs, as well as those with previously diagnosed severe psychiatric conditions. Individuals with folic acid and vitamin B deficiencies, those with any form of anemia, and patients diagnosed with Sjögren syndrome were excluded from the study.

Ethical Considerations

Informed consent was obtained from all participants. The consent form outlined the study's objectives, the right to withdraw at any time, and the provision of necessary medications upon study completion.

Burning Sensation Assessment

A custom numerical scale (0–4) was developed to quantify the burning sensation:
A score of 0 indicated no burning, 1 indicated burning in a single area of the tongue, 2 indicated burning in two distinct areas (such as the tongue and gums, tongue and lips, or tongue and palate), 3 indicated burning in three areas, and 4 indicated burning throughout the mouth(16). This specifically designed scale, which accounted for the geographical distribution of burning in different areas of the mouth, enabled us to identify improvements or deteriorations in burning sensation across various assessments.

Randomization and Intervention

Participants were randomly assigned into four equal groups (n = 10 per group):
The 40 patients were randomly split into four groups of 10 members for each one. The first group of patients received 300 mg / day of pregabalin. In the second group, patients got 600 mg of ALA every day. The third group of patients received combination of ALA and pregabalin daily. The fourth group of patients received 100mg of placebo (sugar pill) daily.

Pain Evaluation and Safety Monitoring

Pain intensity was measured using the Visual Analog Scale (VAS) at baseline, after 1month and at the end of the two-month treatment period. Side effects were recorded during each follow-up visit. Laboratory investigations, including complete blood count and biochemical profiles, were performed at baseline and follow-up to monitor for drug-related adverse effects.
To assess the alterations resulting from the administration of various drugs, it was determined that improvements (positive changes) entailed a reduction in a specific level or numerical category of burning, whereas deteriorations (negative changes) involved an escalation to a higher level of burning. Total resolution signified the complete absence of burning, indicating a transition from any elevated value to a zero value.

Statistical Analysis

The Chi-square test was used to evaluate associations between treatment groups and outcomes, with statistical significance set at $P < 0.05$. Odds ratios were calculated to determine the strength of association between treatment type and burning intensity improvement ($P < 0.01$).

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
https://theaspd.com/index.php

RESULTS

All the participants finished the study since the treatment duration was just 2 months and minor adverse effects were seen. Among the 40 patients examined, 31 were female and 11 were male, with a mean age of 59 ± 13.3. The psychological assessment by using the Hospital Anxiety and Depression Scale (HAD) and confirmation by expert psychiatrist at Erbil Psychiatric Hospital revealed that 35 patients were without pathology (87.5%), 3 exhibited anxiety (7.5%), and 2 presented with depression (5%).

We evaluated alterations in burning levels within each group following one and two months of therapy. During the initial month of treatment, variations in burning levels were independent of the medication type administered (P= 0.293) except for group 4 patients who receives combination of ALA and pregabalin (P=0.039). (Fig.1)

Following two months of therapy, we observed that the favorable alterations in burning levels were strongly influenced by the assigned drug type (P <0.001) (Fig. 2).

Upon examining the changes in patients administered ALA, Pregabalin, or their combination, and comparing them with the changes identified in the placebo group, we noted a significant proportion of individuals exhibiting negative changes within the placebo group. (Fig3)

Four out of ten patients in the ALA group (40%) did not demonstrate improvements, and some experienced exacerbation of burning sensations, whereas the remaining 6 patients (60%) demonstrated positive changes or full recovery. Of the patients treated with pregabalin, 2 out of 10 (20%) showed no change of burning sensation, while the remainder 8 patients (80%) exhibited a reduction or complete absence of burning sensations. Of the participants receiving the combination of both drugs, just one patient out of 10 (10%) exhibited no change, whereas remainder 9 patients (90%) demonstrated positive changes or complete recovery. In the placebo group, 9 out of 10 patients (90%) experienced no change or deterioration, whereas just one patient (10%) exhibited positive changes (Fig.3).

The assessment of odds ratios indicated that the likelihood of exhibiting favorable changes (or complete resolution of the case) for individuals treated with ALA was 13.5 times greater than for those administered a placebo and it was highly significant (P=0.004). Patients administered Pregabalin had a likelihood 36 times greater than the control group and it was strongly significant (P=0.002), whereas those receiving both ALA and Pregabalin demonstrated a likelihood 81 times higher than the control patients and it was strongly significant P<0.001 (Table 1).

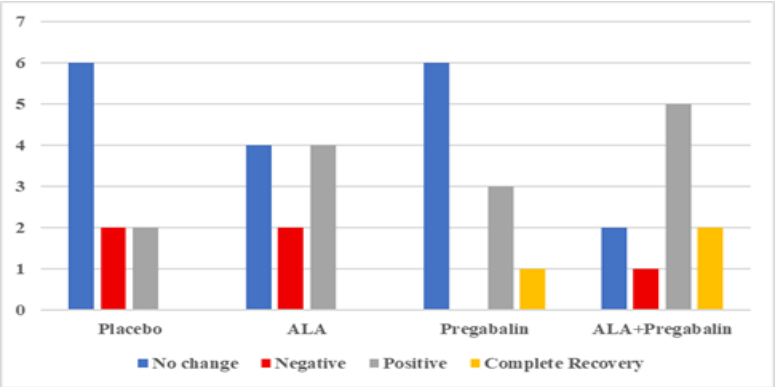

Fig. 1. Analysis of the changes after one month of treatment.

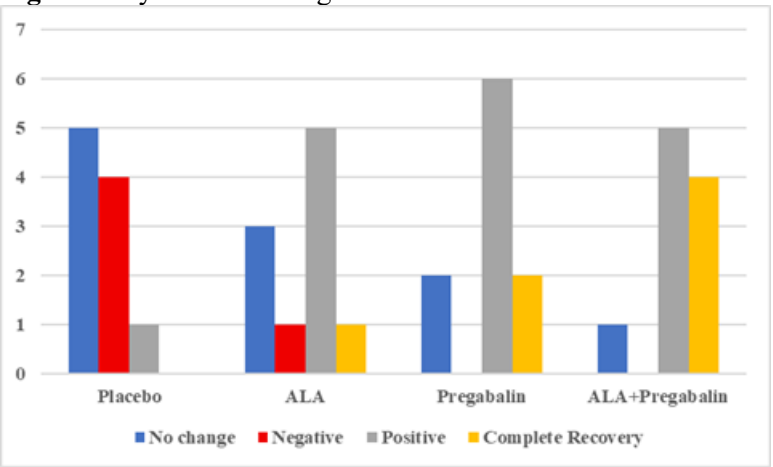

Fig. 2. Analysis of the changes after two months of treatment.

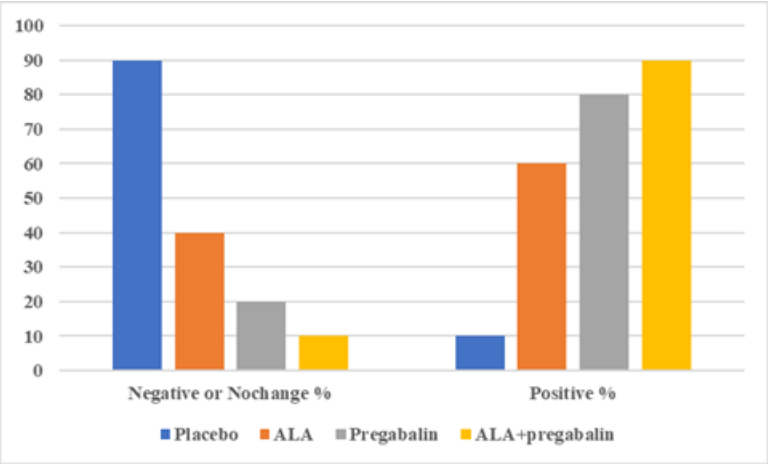

Fig. 3. Comparison of the changes caused by the different drugs after two months.

Table 1. Favorable changes after two months of treatment.

Treatment	Percentage of Favorable Cases	Possibility of Favorable Results
Alpha lipoic Acid (ALA)	60%	13.5 times better
Pregabalin	80%	36 times better
Combination (ALA+Pregabalin)	90%	81 times better

DISCUSSION:

This study investigated the relative effectiveness of alpha-lipoic acid (ALA), pregabalin, and their combination in treating burning mouth syndrome (BMS), a chronic orofacial pain condition of uncertain origin. The results indicate that all three active interventions—ALA, pregabalin, and especially their combination—are significantly more effective than placebo in alleviating the burning feeling linked to BMS(9, 15, 17, 18) .

Our data reflect prior findings that BMS disproportionately impacts women in the postmenopausal demographic, as 77.5% of our participants were female, with a mean age of 59 years. The demographics agree with previous epidemiological research that highlighted hormonal alterations and psychological stressors as important factors to the development of BMS(19, 20).

The psychological assessment revealed a low prevalence of anxiety and depression in this cohort, suggesting that although psychological factors may intensify symptoms, they are not universally present among patients—this conclusion is consistent with recent neurophysiological viewpoints that categorize BMS as a neuropathic disorder rather than solely psychogenic (21, 22).

The enhanced efficacy of pregabalin and ALA compared to placebo is especially significant. Pregabalin, an analog of gamma-aminobutyric acid (GABA), has demonstrated the ability to modify calcium channels and diminish the release of certain neurotransmitters implicated in pain pathways. In our study, 80% of patients with pregabalin exhibited improvement, a result supported by previous research indicating pregabalin's effectiveness in neuropathic pain syndromes, including burning mouth syndrome (13, 15, 23).

Alpha-lipoic acid, a powerful antioxidant with neuroprotective effects, produced positive results, as 60% of patients indicated symptom alleviation. These findings align with other randomized controlled trials that noted a moderate enhancement in BMS symptoms following ALA therapy(10, 12, 24). Nevertheless, many systematic reviews and meta-analyses cautioned against exaggerating ALA's benefits due to inconsistencies in study design and limited sample sizes(10, 11).

The most significant result was noted in the sample administered the combination of ALA and pregabalin, with 90% of patients achieving either partial or total symptom relief. This indicates a potential synergistic effect when both drugs are administered simultaneously—(2, 25). Recent evidence from both

clinical and preclinical studies supports the complementary mechanisms of ALA and pregabalin in neuropathic pain management. While pregabalin modulates central sensitization, ALA contributes to neuronal repair and antioxidant defense. Fixed-dose combinations and meta-analyses suggest enhanced symptom control and quality of life improvements when both agents are used concurrently (25-28).

The odds ratios from our research reinforce this conclusion. The combined therapy resulted in an 81-fold increased probability of good outcomes relative to placebo, greatly surpassing the efficacy of each medicine alone. If confirmed in larger cohorts, this data may offer a persuasive justification for implementing a combined therapy strategy in refractory BMS cases(9, 10, 18, 26-28)

Despite these encouraging results, several limitations must be acknowledged. The modest sample size and short treatment duration may constrain the generalizability and long-term applicability of our findings(29, 30). Although a geographically adapted VAS scoring system was employed to capture nuanced variations in burning sensations, subjective bias remains inherent in pain perception research(31). Furthermore, the exclusion of individuals with significant psychiatric comorbidities may have led to an underestimation of the psychological dimensions influencing therapeutic outcomes(32, 33).

Future research should examine the long-term safety and efficacy of combination therapy, incorporating various dose regimes and stratifying patient subgroups by psychological profiles or systemic comorbidities. Neurophysiological or imaging studies may clarify the mechanisms responsible for symptom improvement, especially for combined antioxidant and neuromodulatory therapy(9, 25, 27, 34)

CONCLUSION

This randomized controlled trial demonstrates that both alpha-lipoic acid and pregabalin significantly alleviate symptoms of burning mouth syndrome, with combination therapy yielding the most substantial benefit. These findings support the neuropathic basis of BMS and suggest a synergistic effect when both agents are used concurrently.

Given the favorable safety profile and promising efficacy, combined ALA and pregabalin therapy may be considered for patients with refractory BMS. However, larger, long-term trials are warranted to confirm these results and establish optimal therapeutic protocols.

These results reinforce the hypothesis that BMS involves a neuropathic component amenable to targeted pharmacotherapy. Both agents were well tolerated, and the dual treatment showed a high rate of favorable outcomes with minimal adverse events.

Limitations include the modest sample size and short follow-up period. Future large-scale, long-term studies are needed to confirm these findings, optimize dosing, and establish standardized treatment guidelines. Ultimately, ALA plus pregabalin may represent a safe, effective option for patients with refractory BMS.

REFERENCES

1. Tan HL, Renton T. Burning mouth syndrome: An update. Cephalalgia Reports. 2020;3:2515816320970143.
2. Adamo D, Spagnuolo G. Burning mouth syndrome: an overview and future perspectives. International journal of environmental research and public health. 2022;20(1):682.
3. Canfora F, Calabria E, Cuocolo R, Ugga L, Buono G, Marenzi G, et al. Burning fog: cognitive impairment in burning mouth syndrome. Frontiers in Aging Neuroscience. 2021;13:727417.
4. Russo M, Crafa P, Guglielmetti S, Franzoni L, Fiore W, Di Mario F. Burning mouth syndrome etiology: a narrative review. Journal of Gastrointestinal and Liver Diseases. 2022;31(2):223-8.
5. Lin X, Jin R, Huang W, Ye Y, Jin J, Zhu W. Trends of burning mouth syndrome: a bibliometric study. Frontiers in Neurology. 2024;15:1443817.
6. Rinaldi F, Gerardi D, Burdo P, Angiolani F, Durate Mendes G, Piattelli M, Varvara G. Burning mouth syndrome: review of etiopathogenetic factors and update on clinical management strategies. ORAL & IMPLANTOLOGY. 2025;17(1):35-43.
7. Egido-Moreno S, Valls-Roca-Umbert J, Perez-Sayans M, Blanco-Carrión A, Jane-Salas E, López-López J. Role of thyroid hormones in burning mouth syndrome. Systematic review. Medicina Oral, Patología Oral y Cirugía Bucal. 2022;28(1):e81.
8. Liu Y, Kim Y, Yoo T, Han P, Inman J. Burning mouth syndrome: a systematic review of treatments. Oral diseases. 2018;24(3):325-34.
9. López-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of Burning Mouth Syndrome: a randomized, double-blind, placebo controlled trial. Med Oral Patol Oral Cir Bucal. 2011;16(5):e635-40.
10. Christy J, Noorani S, Sy F, Al-Eryani K, Enciso R. Efficacy of alpha-lipoic acid in patients with burning mouth syndrome compared to that of placebo or other interventions: a systematic review with meta-analyses. Journal of dental anesthesia and pain medicine. 2022;22(5):323.
11. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. European journal of pain. 2009;13(5):492-6.
12. Alqahtani S. The efficiency of alpha-lipoic acid in the treatment of burning mouth syndrome: a systematic review. European Review for Medical & Pharmacological Sciences. 2021;25(21).

13. Adamo D, Canfora F, Pecoraro G, Leuci S, Coppola N, Marenzi G, et al. Vortioxetine versus SSRI/SNRI with pregabalin augmentation in treatment-resistant burning mouth syndrome: a prospective clinical trial. Current Neuropharmacology. 2025;23(7):800-19.
14. Zhang Q, Tan Z, Ma Q, Guo J, Yang Y. Analysis of pain prognosis, medication efficacy, treatment willingness and influencing factors in patients with burning mouth syndrome: a cross-sectional survey. BMC Oral Health. 2025;25(1):300.
15. Choi S-Y, Choi H, Cho J-G. Effectiveness of Pregabalin in Treatment of Burning Mouth Syndrome. Korean Journal of Otorhinolaryngology-Head and Neck Surgery. 2022;65(11):692-6.
16. Lu C, Zhou X, Yang C, Jiang X, Li X, Huang Z, et al. Efficacy and safety of photobiomodulation combined with oral cryotherapy on oral mucosa pain in patients with burning mouth syndrome: a multi-institutional, randomized, controlled trial. BMC medicine. 2025;23(1):196.
17. Tan HL, Smith JG, Hoffmann J, Renton T. A systematic review of treatment for patients with burning mouth syndrome. Cephalalgia. 2022;42(2):128-61.
18. Çınar SL, Kartal D, Pergel T, Borlu M. Effectiveness and safety of clonazepam, pregabalin, and alpha lipoic acid for the treatment of burning mouth syndrome. Journal of Clinical Practice and Research. 2018;40(1):35.
19. Gupta M, Gupta S. Burning Mouth Syndrome in Postmenopausal Women: A Case-control Study on Hormonal and Psychological Correlates. Journal of Clinical Insights and Research in Dentistry. 2025;1(1):9-13.
20. Blackson EA, McCarthy C, Bell C, Ramirez S, Bazzano AN. Experiences of menopausal transition among populations exposed to chronic psychosocial stress in the United States: a scoping review. BMC Women's Health. 2024;24(1):487.
21. Orliaguet M, Misery L. Neuropathic and psychogenic components of burning mouth syndrome: a systematic review. Biomolecules. 2021;11(8):1237.
22. Carreño-Hernández I, Cassol-Spanemberg J, de Rivera-Campillo ER, Estrugo-Devesa A, López-López J. Is burning mouth syndrome a neuropathic pain disorder? A systematic review. J Oral Facial Pain Headache. 2021;35:218-29.
23. Onakpoya IJ, Thomas ET, Lee JJ, Goldacre B, Heneghan CJ. Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomised clinical trials. BMJ open. 2019;9(1):e023600.
24. Palacios-Sánchez B, Moreno-López L-A, Cerero-Lapiedra R, Llamas-Martínez S, Esparza-Gómez G. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. Medicina oral, patologia oral y cirugia bucal. 2015;20(4):e435.
25. Gilron I, Robb S, Tu D, Holden RR, Jackson AC, Duggan S, Milev R. Randomized, double-blind, controlled trial of a combination of alpha-lipoic acid and pregabalin for neuropathic pain: the PAIN-CARE trial. Pain. 2024;165(2):461-9.
26. Kandala S. Justification for Fixed Dose Combination (FDC) of Pregabalin 75mg+ Methylcobalamin 750mcg+ Alpha lipoic acid USP 100mg+ Folic acid 1.50 mg Capsule.
27. Nozawa K, Karasawa Y, Shidahara Y, Ushida T. Efficacy of Combination Therapy with Pregabalin in Neuropathic Pain: A Preclinical Study in the Rat L5 Spinal Nerve Ligation Model. Journal of Pain Research. 2022:3469-78.
28. Freeman R, Durso-DeCruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes care. 2008;31(7):1448-54.
29. López Jornet MP, Camacho Alonso F, Andujar Mateos P, Sánchez Siles MA, Gómez García FJ. Burning mouth syndrome: an update. 2010.
30. He Y, Lin Y, He X, Li C, Lu Q, He J. The conservative management for improving Visual Analog Scale (VAS) pain scoring in greater trochanteric pain syndrome: a Bayesian analysis. BMC Musculoskeletal Disorders. 2023;24(1):423.
31. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. Academic emergency medicine. 2003;10(4):390-2.
32. Mitsikostas DD, Ljubisavljevic S, Deligianni CI. Refractory burning mouth syndrome: clinical and paraclinical evaluation, comorbidities, treatment and outcome. The journal of headache and pain. 2017;18(1):40.
33. Ţ¸enea-Cojan Ş¸-T, Dinescu V-C, Gheorman V, Dragne I-G, Gheorman V, Forţ¸ofoiu M-C, et al. Exploring multidisciplinary approaches to comorbid psychiatric and medical disorders: A scoping review. Life. 2025;15(2):251.
34. Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Julious S, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. The Lancet. 2022;400(10353):680-90.