injury to the right hand, experienced good pain reduction to low-dose intravenous immunoglobulin treatment, which was repeatable, but did not induce remission [4]. Her pain intensity was reduced from NRS 6 to NRS 3 after one TPE treatment cycle (five ETs); limb swelling and color changes normalized. She has remained in remission, with only mild pain and intermittent tramadol medication use until today (6 years later).
5. There was no improvement after five ETs in a 36-year-old woman with CRPS in both lower legs and problematic leg ulcerations.
6. Mild pain reduction was reported (a reduction from NRS 8 to NRS 7) lasting 1 week, alongside normalization of autonomic signs, by a 35-year-old women with leg CRPS of 8-year duration. The change started 2 weeks after her sixth and last ET. There were no effects on mood or fatigue, and she did not consider this TPE effect meaningful.

Treatment-related side effects included one central venous line infection requiring line exchange and treatment with vancomycin × 7 days, post-ET tiredness, headaches, and one episode of chest pain not requiring further management.

In this first report of TPE treatment in long-standing CRPS, patient responses were variable. In some cases, maximal pain reduction started with time delay and was incomplete (Patients 1 and 6); this suggests that further ETs in these patients may achieve additional benefit. Remarkably, 3/6 patients (patients 1, 2, and 3) reported that meaningful improvements of mood and fatigue either preceded the onset of analgesia or were the sole treatment effect.

We present preliminary evidence that TPE may be effective in long-standing CRPS. Future prospective trials should allow the application of additional ETs within the same treatment cycle, in patients who either have not or have only partially responded to five to seven ETs after 2 weeks. The role of serum factors that cause low mood and fatigue in these patients, and the brain signature of patients with TPE-induced improved mood, without analgesia, also deserve further study.

TPE treatment appeared to induce remission in some patients, but for others, repeat TPE treatment may not always be feasible, so the efficacy of immunosuppressant treatments should also be investigated in this group. Our results add further credence to the concept that serum factors contribute to causing and/or maintaining some of the long-standing symptoms of CRPS.

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The Effect of Clonazepam Mouthwash on the Symptomatology of Burning Mouth Syndrome: An Open Pilot Study

Disclosure: The authors declare that they have no conflict of interest.

Dear Editor,

Burning mouth syndrome (BMS) is a chronic idiopathic disorder characterized by burning sensation or dysesthesia in the tongue and other oral sites without clinical and laboratory findings, often accompanied by dry mouth, tingling, or dysgeusia. There is no standard recognized treatment. Considering the peripheral nervous alterations identified in BMS patients, some clinical trials have demonstrated the efficacy of topical clonazepam on BMS symptoms [1,2]. This study aimed to investigate

Table 1 Outcomes of clonazepam mouthwash on BMS symptoms

Response	N (%)
Worsening	0 (0)
Same (no difference)	6 (33.3)
Slight improvement (until 50% of remission)	3 (16.7)
Moderate improvement (50–80% of remission)	6 (33.3)
Marked improvement ($\geq$80% of remission)	1 (5.6)
Complete remission	2 (11.1)
Total	18 (100)

BMS = burning mouth syndrome.

the effect of clonazepam mouthwash on BMS symptomatology.

The efficacy of topical clonazepam has been demonstrated in previous studies [1,2] where the drug was administrated as a mouth dissolving tablet. In addition, recent findings from an experimental animal study [3] demonstrated the presence of GABA A receptors in the tongue nerve fibers of rats. As benzodiazepines bind to GABA A receptors, these findings support the hypothesis that clonazepam acts locally in the oral mucosa reducing pain in BMS patients [3]. Other studies in human oral mucosa are needed to confirm this hypothesis.

Other drugs as benzydamine hydrochloride [4] and capsaicin [5] have been tested as mouthwash formulations to treat BMS. However, the results did not prove to be satisfactory as therapeutic options. The use of benzydamine hydrochloride oral rinse was notably unable to reduce the burning sensation in BMS patients [4], while the capsaicin solution was effective but poorly tolerated as one-third of the patients complained of intense burning during and for a few minutes after application of the capsaicin mouthwash [5].

This is the first study designed to examine the clinical efficacy of clonazepam as an oral rinse preparation. Mouthwash formulations have several advantages since the drug can be applied more uniformly to the entire mouth, and a pleasant flavor can be added to the mouthwash to enhance compliance.

The study was approved by the local ethics committee. Sixteen participants complaining of burning tongue and two participants reporting burning in gingivae and palate were enrolled. All subjects underwent a comprehensive clinical assessment, and as there were no identifiable causes of oral burning after anamnesis, physical examination, and laboratory tests, a final diagnosis of primary BMS was made for all 18 patients. Participants were treated three times daily over a 14-day period with 10 mL of topical clonazepam (oral rinse solution 1 mg/10 mL) for 3 minutes, after which the solution was expectorated. Burning intensity was assessed by a visual analogue scale (VAS) ranging from 0 (no burning) to 10 (intolerable burning). VAS values were assessed at baseline and after treatment on the 15th day.

The clinical profile of the patients is in accordance with the epidemiological data on BMS as our sample was predominantly composed of females (17/18–94%) and had a mean age of 59 years (range, 30–75 years), and over half reported chronic burning accompanied by xerostomia (12/18–67%), tingling (12/18–67%), and dysgeusia (10/18–56%). Half of the patients (9/18) reported symptom duration lasting from 1 to 3 years.

Our results suggest that clonazepam mouthwash resulted in significant improvement in BMS symptomatology, given that participant's mean VAS scores went from 5.56 ± 2.77 before treatment to 3.50 ± 3.19 afterwards ($P = 0.002$, Wilcoxon test). Twelve (66.7%) reported symptom improvement, ranging from slightly beneficial to complete remission, while the symptoms of six (33.3%) participants remained unchanged (Table 1). There were no reports of adverse effects during the study. We could not find correlations between the outcomes and other variables such as age, time since diagnosis, and additional symptoms (xerostomia, tingling, and dysgeusia).

It is noteworthy that one-third of study patients did not respond to treatment. One possible explanation could be the existence of two BMS subgroups [6], central and peripheral, depending on the main location of the neuropathic alterations. Thus, those who did not respond to topical clonazepam in the current study might belong to the central subgroup. Despite the limitations of this study, mainly the lack of a placebo control group, our preliminary results suggest that clonazepam mouthwash can serve as a safe and effective therapeutic modality in a subset of BMS patients. Future randomized clinical trials in this field are warranted.

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